Optimisation de l'antibiothérapie : de la pharmaco-cinétique aux nouveaux modes d'administration

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JCOR. Hammamet 28 Mai 2016

Connectez-vous

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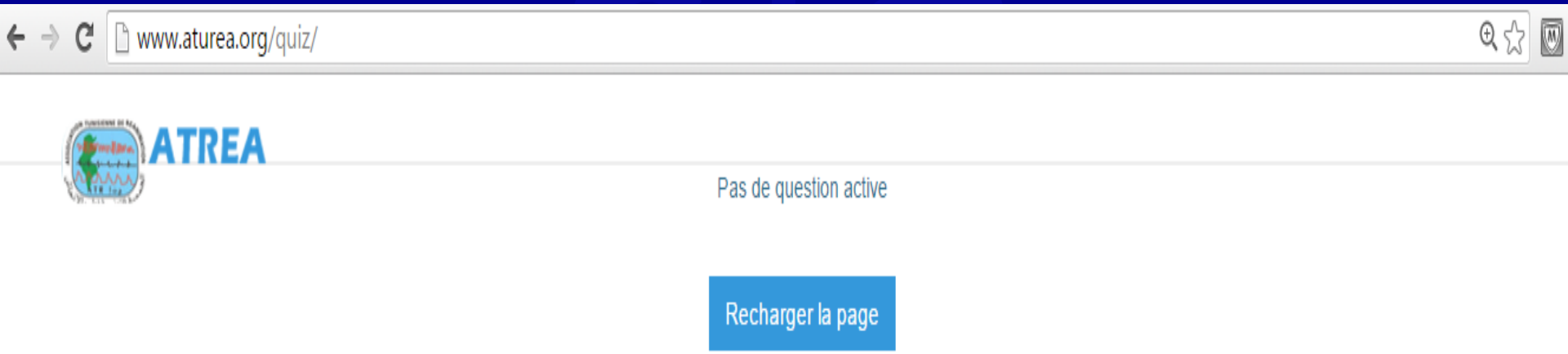


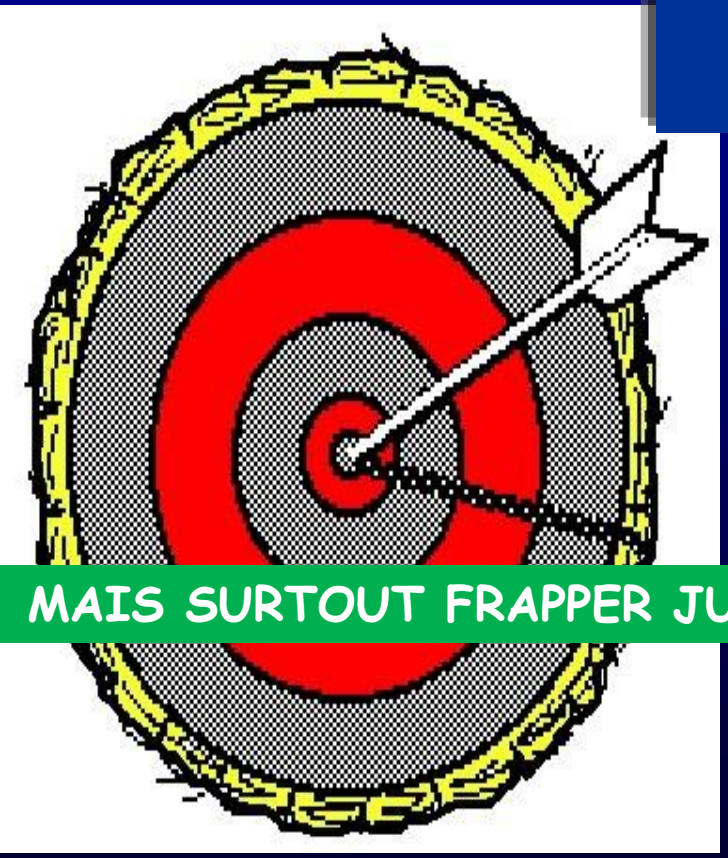
Pourquoi ?

Savoir ne pas les prescrire

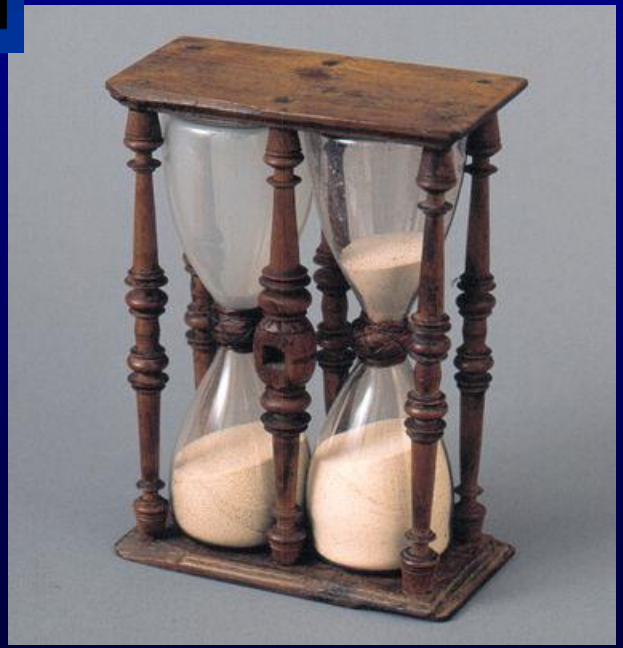
- Pas d'ATB sans diagnostic d'infection bactérienne
  - Confirmé ou suspecté → syndrome + site ± bactérie
  - Fièvre, CRP élevée, ECBU +, n'est pas synonyme d'infection
- Pas d'ATB sans prélèvements,
  - Sauf exception:
    - Urgence (purpura fulminans),
    - Critères définis (exacerbation BPCO sévère, cystite…)

Antibiothérapie c'est un pari qu'il faut impérativement gagner !!

FRAPPER FORT



MAIS SURTOUT FRAPPER JUSTE



FRAPPER VITE

- L'antibiothérapie que l'on est amené à prescrire devant un état infectieux grave, obéit à certaines contraintes :
  - Adaptée au(x) germe(s) et à sa (ou leur) localisation(s)
  - Elle doit obtenir une activité rapidement bactéricide au site de l'infection pour réduire l'inoculum bactérien et limiter la diffusion systémique de l'infection
  - Les critères de choix s'appuient donc sur:
    - L'origine et l'épidémiologie de l'infection
    - Sur les critères pharmacocinétiques (PK) et pharmacodynamiques (PD) des antibiotiques
      - Pharmacocinétique : rapport entre les posologies administrées les concentrations obtenues et leurs variations au cours du temps. Elle permet de définir la CMI, la CMB et l'effet post antibiotique

Question 1 :

VOTEZ

L'antibiothérapie empirique :

1. Est synonyme d'une antibiothérapie probabiliste
2. Nécessite des prélèvements microbiologiques au préalable
3. Nécessite obligatoirement une adaptation
4. Toutes les propositions sont justes
5. Toutes les propositions sont fausses

Question 1 :

Est administrée obligatoirement après prélèvements microbiologiques et nécessite une adaptation

L'antibiothérapie empirique :

1. Est synonyme d'une antibiothérapie probabiliste
2. Nécessite des prélèvements microbiologiques au préalable
3. Nécessite obligatoirement une adaptation
4. Toutes les propositions sont justes
5. **Toutes les propositions sont fausses**

Peut nécessiter (limite) une réévaluation

Question 2 :

L'activité antibactérienne d'un antibiotique est caractérisée en pratique par :

1. La CMI
2. La demi-vie sérique
3. La CMB
4. L'effet post antibiotique
5. Toutes les propositions sont justes

VOTEZ

Question 2 :

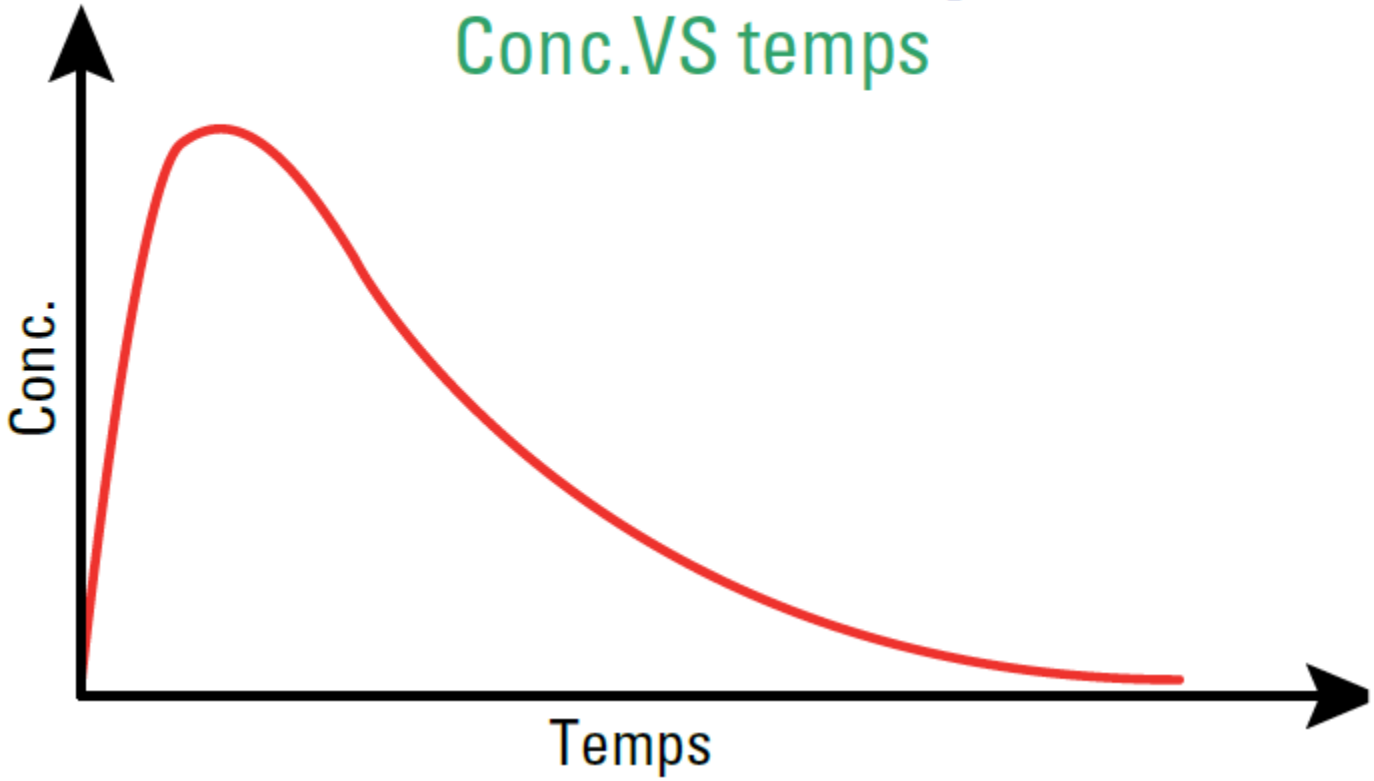
L'activité antibactérienne d'un antibiotique est caractérisée en pratique par :

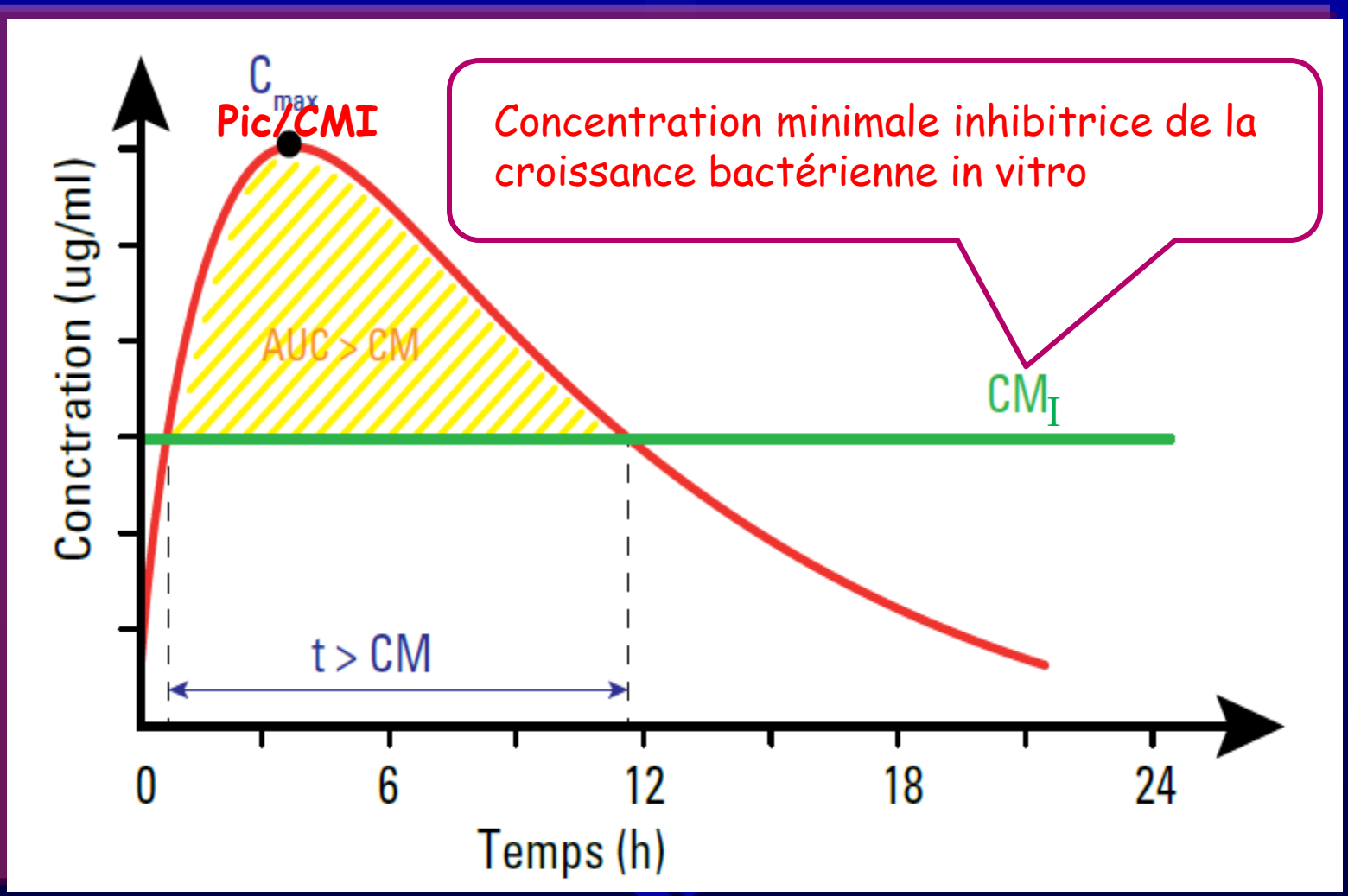
1. **La CMI** — Concentration minimale inhibitrice de la croissance bactérienne in vitro
2. La demi-vie sérique
3. La CMB — Concentration minimale bactéricide laissant un nombre de survivant ≤ 0.01% de l'inoculum bactérien de départ
4. L'effet post antibiotique
5. Toutes les propositions sont justes

Délai de recroissance bactérienne après exposition à l'antibiotique

Pharmacocinétique

Conc.VS temps




C max
Pic/CMI
Concentration minimale inhibitrice de la croissance bactérienne in vitro
AUC > CM
CMI
Conctration (ug/ml)
t > CM
0
6
12
18
24
Temps (h)

Question 3

Parmi les paramètres suivants, quels sont ceux qui sont associés à l'activité des antibiotiques?

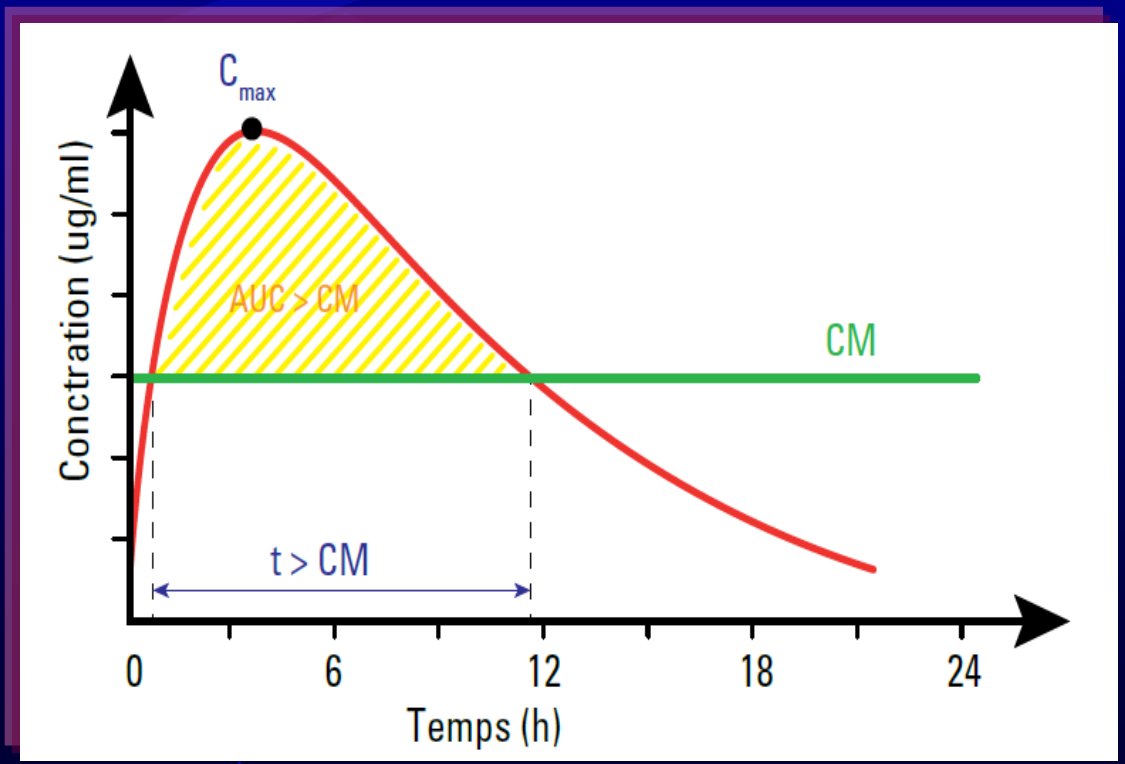
1. T > CMI
2. Pic
3. Pic/CMI
4. ASC
5. ASC/CMI

VOTEZ

Question 3

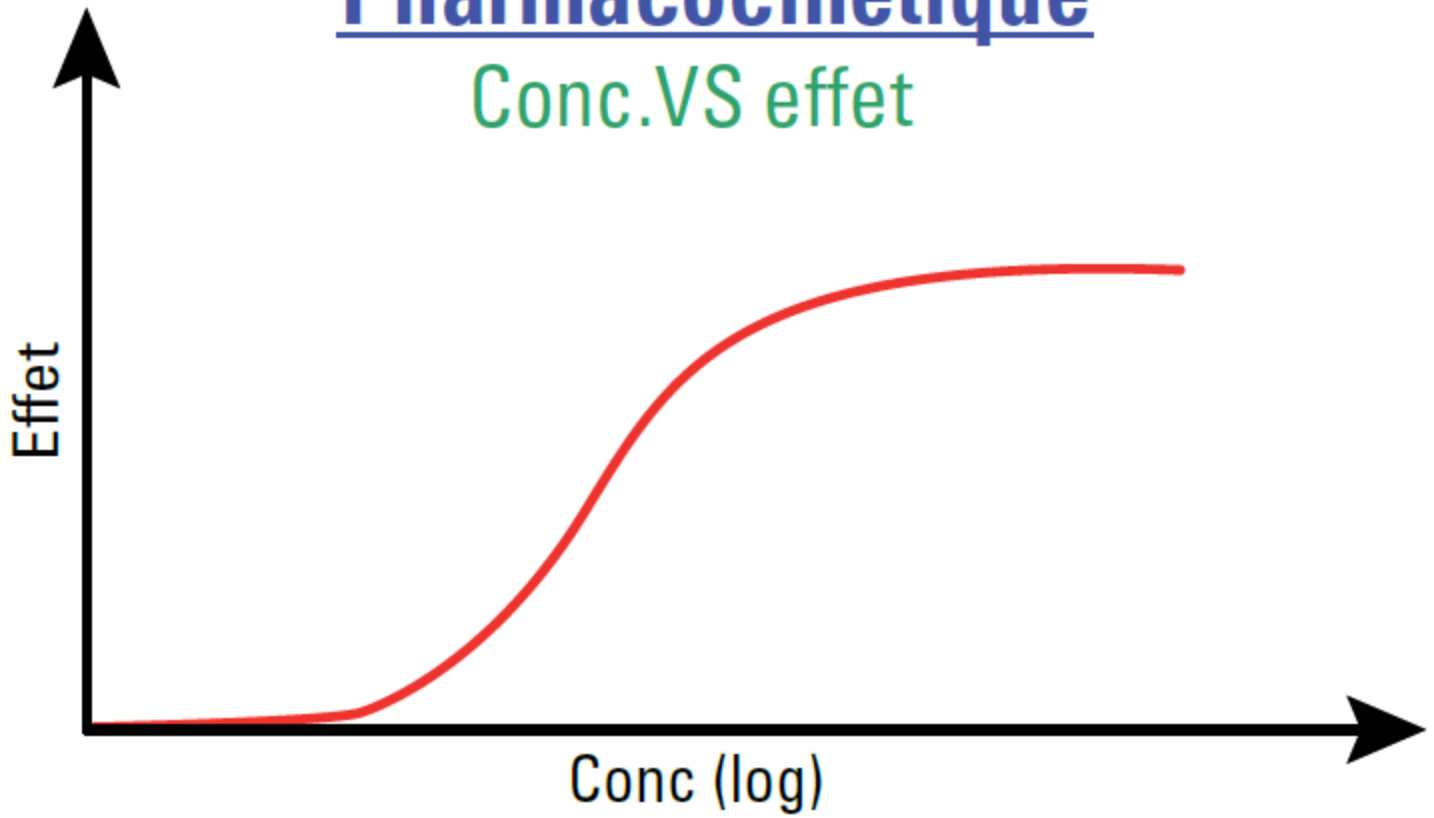
Parmi les paramètres suivants, quels sont ceux qui sont associés à l'activité des antibiotiques?

1. **T > CMI**
2. Pic
3. **Pic/CMI**
4. ASC
5. **ASC/CMI**



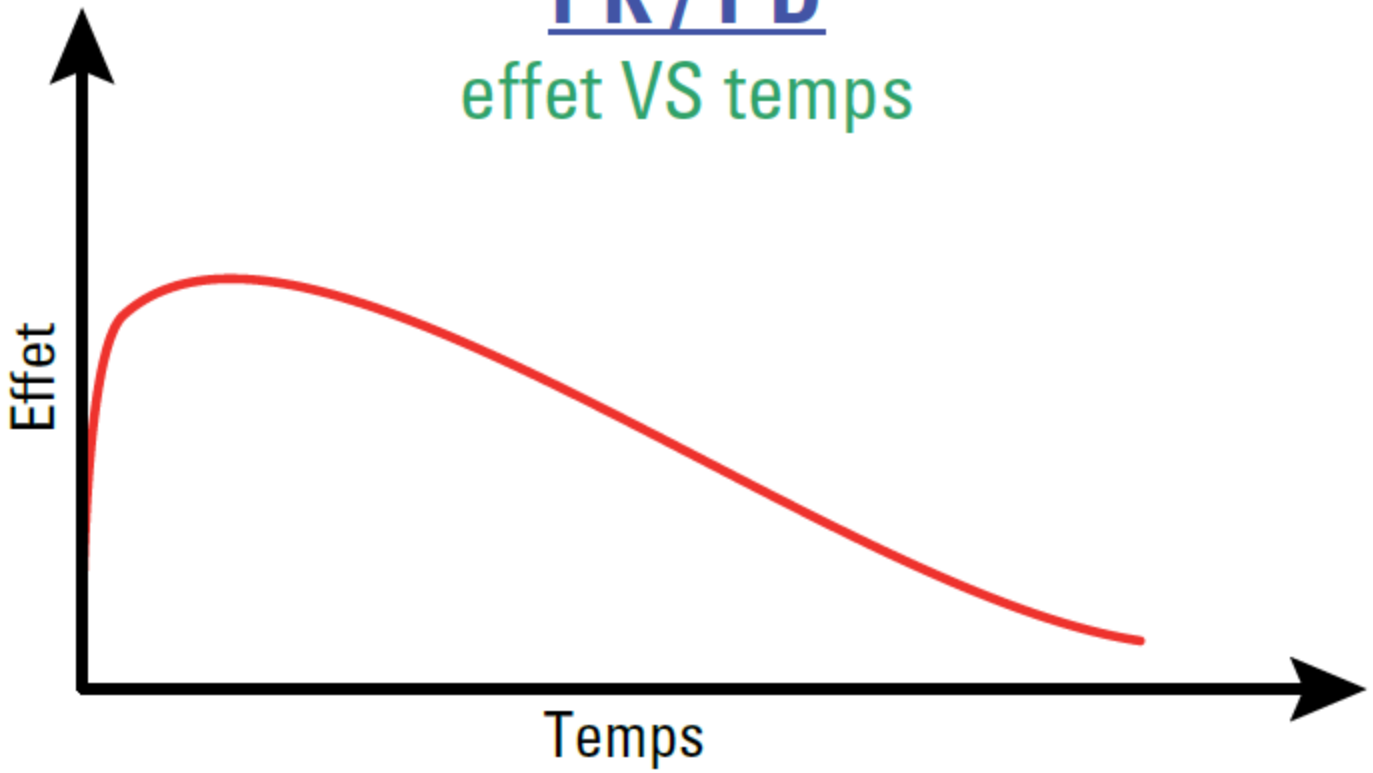
Pharmacocinétique

Conc.VS effet



PK / PD

effet VS temps



Question 4

Parmi les paramètres PK/PD suivants, quelles sont ceux qui peuvent être impliqués dans la prévention de l'émergence de résistance?

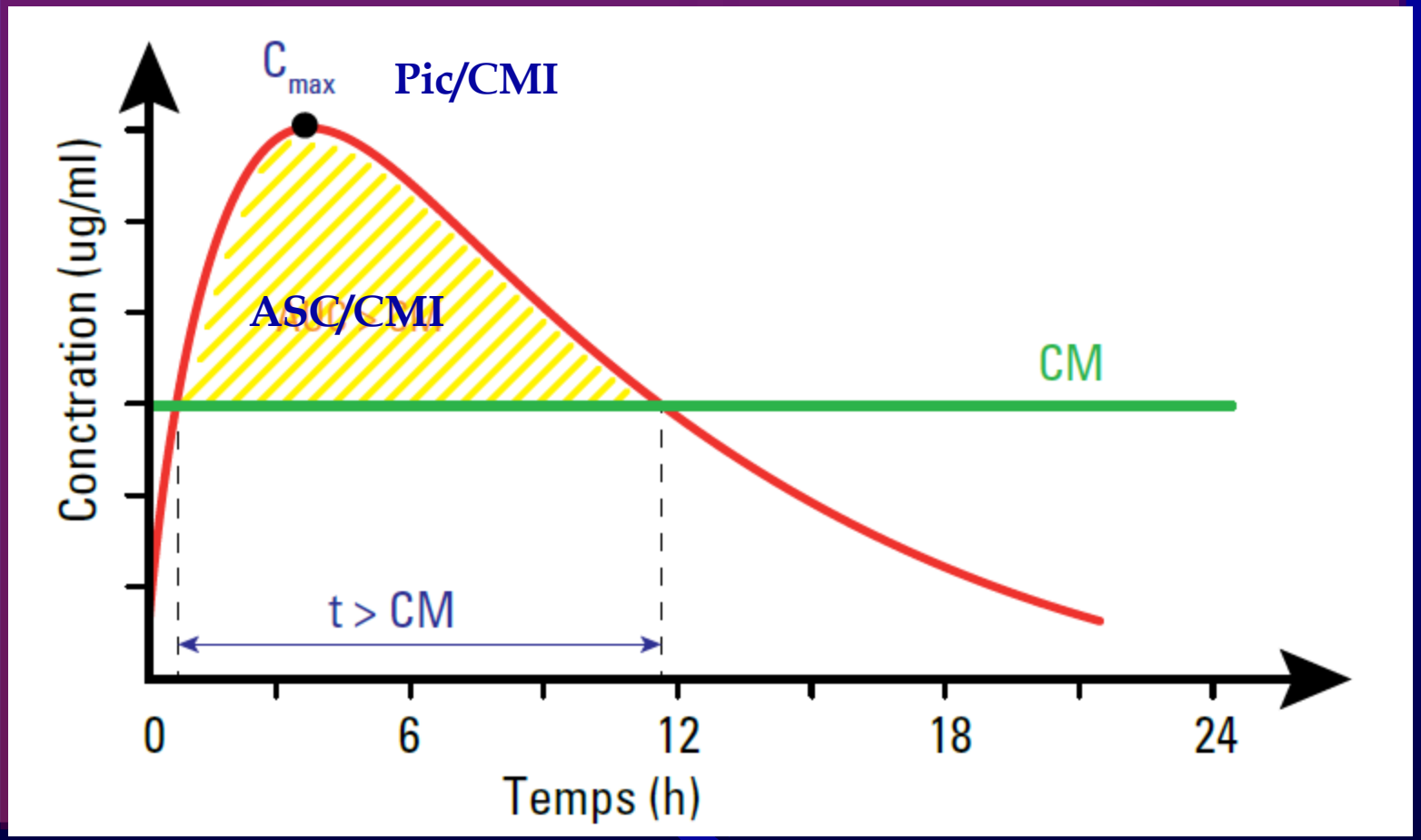
VOTEZ

1. ASC/CMI
2. Concentration résiduelle/CMI
3. Pic/CMI
4. Concentration de prévention des mutants
5. Toutes les proposition sont justes

Question 4

Parmi les paramètres PK/PD suivants, quelles sont ceux qui peuvent être impliqués dans la prévention de l'émergence de résistance?

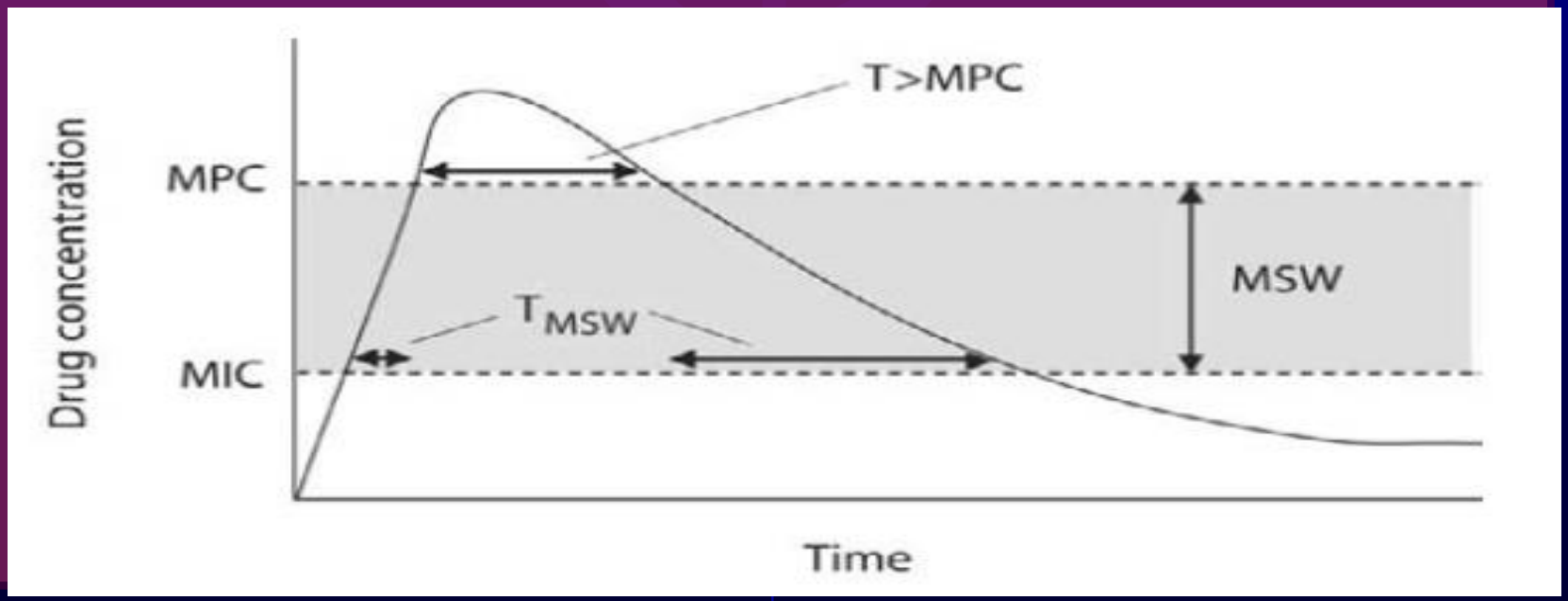
1. **ASC/CMI**
2. Concentration résiduelle/CMI
3. **Pic/CMI**
4. **Concentration de prévention des mutants**
5. Toutes les proposition sont justes


C max
Pic/CMI
ASC/CMI
CM
Conctration (ug/ml)
t > CM
0
6
12
18
24
Temps (h)

Concentration de prévention des mutants (CPM)

Antibiotic Dosage and Resistance • CID 2007:45 (Suppl 2)

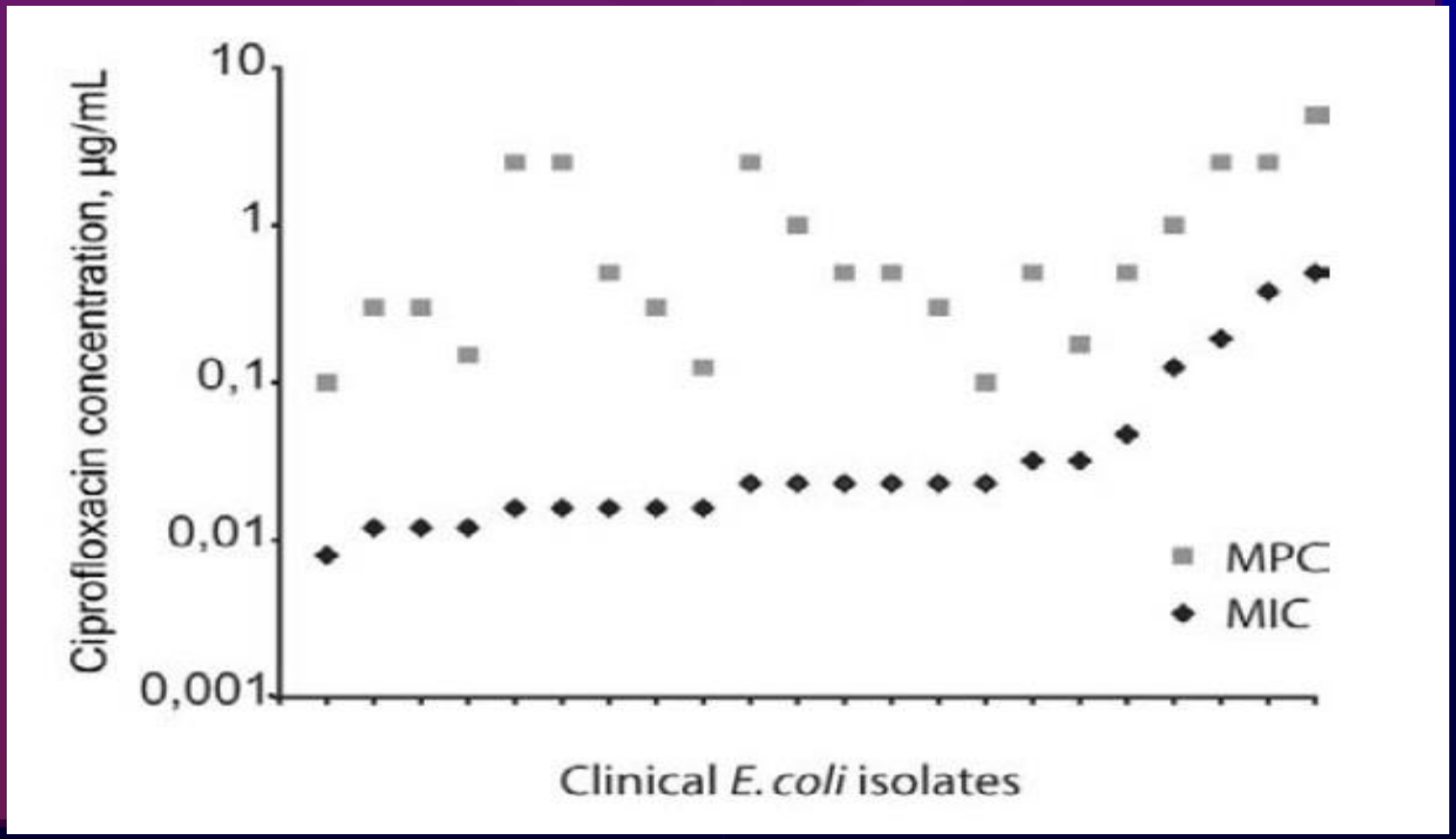
- Elle est toujours supérieure à la CMI
- C'est la CMI de la sous population la plus résistante dans une population bactérienne hétérogène



Concentration de prévention des mutants (CPM)

Antibiotic Dosage and Resistance • CID 2007:45 (Suppl 2)

- Elle est toujours supérieure à la CMI
- Elle est généralement proportionnelle à la CMI



Bien utiliser les antibiotiques

- Posologie:
  - Les sous dosages sont dangereux
  - Rythme d'administration
    - Propriétés PK/PD des molécules
    - 1, 2, 3, 4 x/j ou SAP/24h ?

- Utiliser le mode d'administration le plus adéquat

Deux grandes familles d'antibiotiques

- Concentration- dépendants
  - Pic élevé >>> CMI — Cmax/CMI
  - Aminosides — ASC/CMI
  - Fluoroquinolones
- Temps-dépendants — T (% 24h) > CMI
  - Concentration le plus lgtps possible > CMI /24h
    - Soit: 3-4 administrations / j
      - Bêtalactamines sauf CFTX, pyostacine, vanco
    - Soit: demi vie longue: 1 à 2 / j
      - Macrolides, CFTX, teicoplanine

Garnacho-Montero *et al. BMC Infectious Diseases* 2014, **14**:135
http://www.biomedcentral.com/1471-2334/14/135

BMC Infectious Diseases

REVIEW Open Access

How to treat VAP due to MDR pathogens in ICU patients

José Garnacho-Montero[1,2,3*], Yael Corcia-Palomo[1], Rosario Amaya-Villar[1,3] and Luis Martin-Villen[1]

Table 2 Recommended doses of antimicrobials use in VAP caused by MDR pathogens in patients with normal renal function

Antibiotic	Loading dose	Daily dose	Observations
Imipenem*	Not required	1 g/6-8 h	Extended or prolonged infusion is not possible due to drug instability
Meropenem*	Not required	1-2 g/8 h	Extended infusion (3-4 hours) is recommended.
Doripenem*	Not required	500 mg-1 g/8 h	Extended infusion (3-4 hours) is recommended.
Colistin*	4.5-9 UI	9 UI/day in 2 or 3 dose	Loading dose is necessary.
Tigecycline	200 mg	100 mg/ 12 h	Without approval by regulatory agencies.
Fosfomycin*	Not required	24 g/day (in four doses)	Always in combination therapy.
Vancomycin*	25-30 mg/kg (based on ABW)	15-20 mg/kg (based on ABW) every 8-12 hours	Monitor trough concentrations after the forth dose; serum trough levels of 15-20 mg/L for MRSA VAP.
Linezolid	Not required	600 mg/ 12 h	It should be changed to vancomycin in the directed therapy of patients with good clinical evolution and *S aureus* with vancomycin MIC ≤ 1 mg/L

*Dose adjustment is necessary in case of renal dysfunction.

Conclusions: Empirical treatment of VAP due to MDR pathogens should be based on knowledge of local ecology. A strategy combining early high doses of effective agents with subsequent simplification in the light of microbiologic information is recommended.

De Pascale *et al. Critical Care* 2014, **18**:R90
http://ccforum.com/content/18/3/R90

CRITICAL CARE

RESEARCH Open Access

High dose tigecycline in critically ill patients with severe infections due to multidrug-resistant bacteria

Gennaro De Pascale[1*], Luca Montini[1], Mariano Alberto Pennisi[1], Valentina Bernini[1], Riccardo Maviglia[1], Giuseppe Bello[1], Teresa Spanu[3], Mario Tumbarello[2] and Massimo Antonelli[1]

- Tous les patients : Juin 2009 juin 2012 qui ont reçu TGC pour une infection documentée ont été évalués.

Table 3 Logistic regression analysis of factors associated with clinical cure in 63 patients with ventilator-associated pneumonia

Variable	Multivariate analysis		
	Odds ratio	95% CI	*P*-value
SOFA score at infection occurrence	0.66	0.51, 0.87	0.003
Initial inadequate treatment	0.18	0.05, 0.68	0.01
High-dose tigecycline group	6.25	1.59, 24.57	0.009

Conclusions

These data suggest that TGC, used at doses higher than standard treatment, can be administered without relevant toxicity for the treatment of serious infections in critically ill sedated patients. The regimen with higher TGC doses (that is, 100 mg every 12 hours after a 200 mg loading dose) may be useful to improve the clinical outcome of patients with MDR Gram-negative VAP. Pharmacokinetic investigations and multicenter, prospective clinical trials are needed to confirm these preliminary results and investigate the efficacy of HD TGC in severe infections.

Antimicrobial Section / Original Paper

Chemotherapy

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Efficacy and Toxicity of High-Dose Colistin in Multidrug-Resistant Gram-Negative Bacilli Infections: A Comparative Study of a Matched Series

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Mouna Oueslati Rahma Mannai Montassar Bouzidi Salah Ben Lakhal

Medical Intensive Care Unit, University Hospital Center of La Rabta, Tunis, Tunisia

- The study was conducted at the Medical Resuscitation Unit, Tunisian University Hospital Center of La Rabta,
  - over a period of 17 months (April 2013 to August 2014)
- In the high-dose colistin group,
  - CMS was administered at a loading dose of 9 MIU followed by a maintenance dose of 4.5 MIU/12 h.
- In the second group, retrospectively analyzed, colistin was administered at 6 MIU/day.

Table 1. Clinical characteristics of patients

	High-dose colistin group (n = 46)	Standard-dose colistin (n = 46)	p value

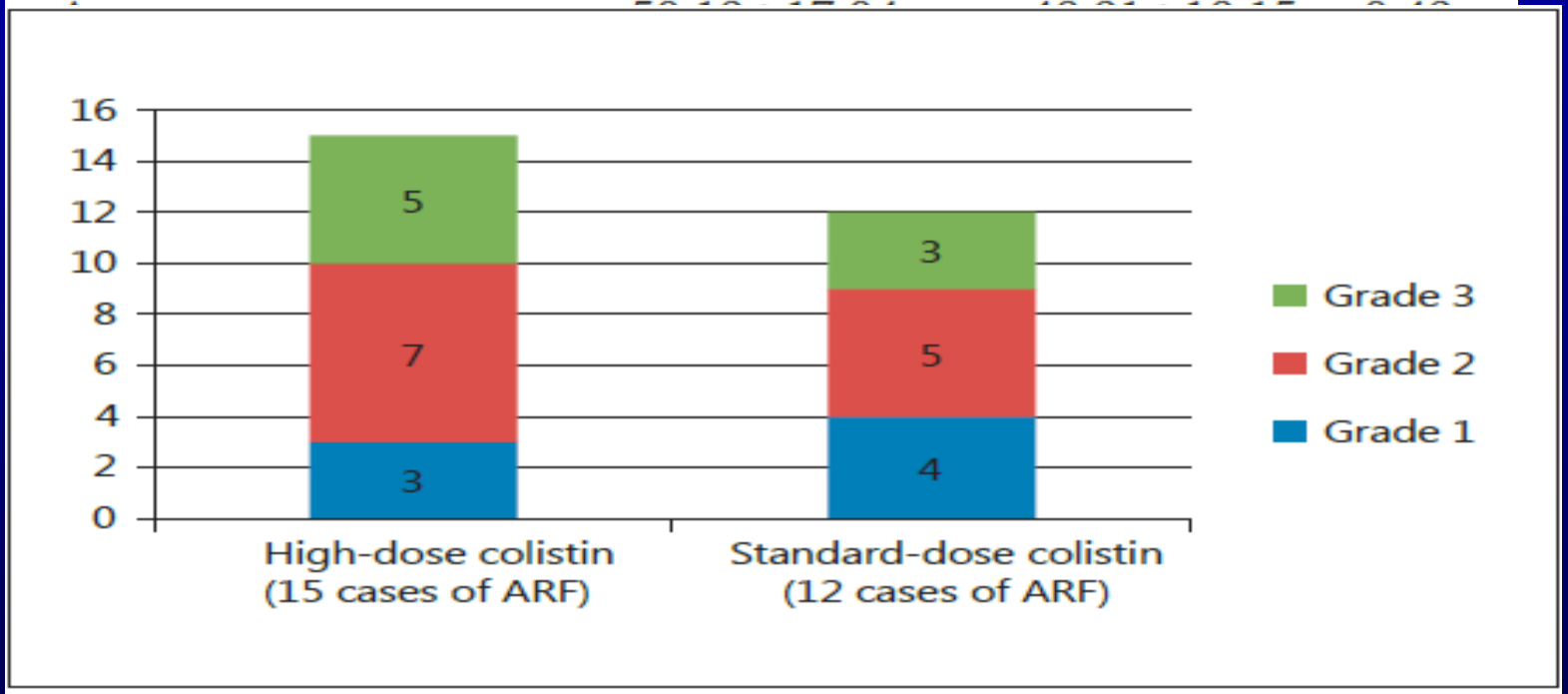


Fig. 2. Distribution of patients in the 2 groups according to the AKIN classification. ARF = Acute renal failure.

Table 2. Outcome parameters of the 2 groups

Studied variables	High-dose colistin group (n = 46)	Standard-dose colistin group (n = 46)	p value
Cure rate	63	41.3	0.04
Duration of treatment, days	13.63±8.1 (12)	15.63±6.3 (15)	0.25
Recurrent infection	4.3	13	0.21
AKI	32.2	26	0.64
Time to AKI onset, days	8.32±4.3 (7)	11±6.4 (9.5)	1
Renal replacement therapy	26.6	41	1
Neurotoxicity	6.5	2.1	0.25
Mortality	23	27.5	0.6

Values are expressed as percentages or mean ± standard deviation (median).

Question 5

La perfusion continue des béta-lactamines

1. Est justifiée par une ½ vie souvent courte pour ces molécules
2. Vise à augmenter le T > CMI
3. A démontré une réduction de la mortalité
4. Permet de limiter la variabilité des concentrations en réanimation
5. Toutes les proposition sont justes

VOTEZ

Question 5

La perfusion continue des béta-lactamines

1. **Est justifiée par une ½ vie souvent courte pour ces molécules**
2. **Vise à augmenter le T > CMI**
3. A démontré une réduction de la mortalité
4. **Permet de limiter la variabilité des concentrations en réanimation**
5. Toutes les proposition sont justes

Question 6

Quel(s) antibiotique(s) parmi les suivants a(ont) une pénétration alvéolaire d'environ 100%

1. Ceftazidime
2. Lévofloxacine
3. Linézolide
4. Vancomycine

VOTEZ

Question 6

Quel(s) antibiotique(s) parmi les suivants a(ont) une pénétration alvéolaire d'environ 100%

1. Ceftazidime
2. **Lévofloxacine**
3. **Linézolide**
4. Vancomycine

Bien utiliser les antibiotiques

- Posologie:
  - Les sous dosages sont dangereux
  - Respecter rythme d'administration

- Voie et modalités d'administration
  - PO: infections peu sévères si pas de troubles de déglutition ou d'absorption
  - IV = PO si bioéquivalentes
  - IM et antibiothérapie locale à proscrire sauf rares situations
  - Aérosols

Pourquoi nébuliser des antibiotiques? Rationnel

- La pénétration pulm de certains ATB par voie IV est faible

Experimental ICU Study Group: Nebulized ceftazidime in experimental pneumonia caused by partially resistant Pseudomonas aeruginosa. Ferrari F, Lu Q, Girardi C, et al, Intensive Care Med 2009; 35:1792–800

- Dépôt alvéolaire → action in situ plus rapide et à concentrations plus élevées → → bactéricidie locale rapide

Treatment of carbapenem-resistant Acinetobacter baumannii ventilator-associatedpneumonia: retrospective comparison between intravenous colistin and intra-venous ampicillin–sulbactam. Zalts R, et al. Am J Ther 2013

Pourquoi nébuliser des antibiotiques? Rationnel

- Faible passage systémique

The use of inhaled antibiotic therapy in the treatment of ventilator-associated pneumonia and tracheobronchitis: a systematic review. Russell et al. BMC Pulmonary Medicine (2016) 16:40

- La flore digestive est probablement moins altérée par l'inhalation que par l'administration systémique

Palmer LB, Smaldone GC. Reduction of bacterial resistance with inhaled antibiotics in the intensive care unit. Am J Respir Crit Care Med. 2014;189:1225â€“33.

Pourquoi nébuliser des antibiotiques? Rationnel

- Délivrer directement le médicament au site infecté, donc assurer une bactéricidie locale optimale:

  - **Aminosides: tobramycine, amikacine,**
  - **B lact: Ceftazidime, Aztreonam**
  - **Colistine**
  - **Fosfomycine**
  - ----------

Règles de Nébulisation

La livraison d'ATB dans les alvéoles exige:

- Nébulisation adéquate des antibiotiques :
  - taille appropriée des particules
  - à des concentrations élevées.

- Nébuliseur adéquat (VM): les Nébuliseurs pneumatiques (ou à jet) sont moins efficaces à la livraison d'ATB que d'autres méthodes: nébuliseurs à plaques ultrasoniques (ou à tamis vibrant)

Hallal A et al. Aerosolized tobramycin in the treatment of ventilator-associated pneumonia: a pilot study. Surg Infect (Larchmt). 2007;8:73â€“82.

Niederman MS, Chastre J, Corkery K, Fink JB, Luyt CE, Garcia MS. B551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia. Intensive Care Med. 2012;38:263â€“

Palmer LB, Smaldone GC, Chen JJ, Baram D, Duan T, Monteforte M, et al. Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. Crit Care Med. 2008;36:2008â 13.

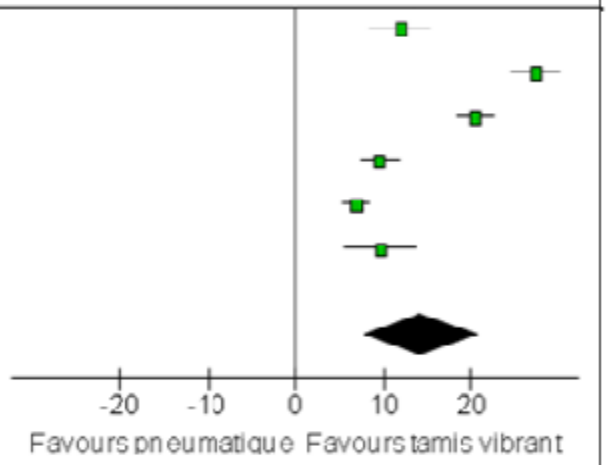
Haute Ecole de Santé Vaud Physiothérapie 2013

NEBULISATION EN VENTILATION MECANIQUE INVASIVE ET NON-INVASIVE (SANS SYSTEME D'HUMIDIFICATION). COMPARAISON « IN VITRO » DES DOSES EMISES PAR DEUX TYPES DE NEBULISEURS : NEBULISEUR PNEUMATIQUE VERSUS NEBULISEUR A TAMIS VIBRANT

Study or Subgroup	tamis vibrant Mean	SD	Total	pneumatique Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abdelrahim / Position 2 VNI	18.71	5.466	10	6.82	1.39	10	16.4%	11.89 [8.39, 15.39]
Abdelrahim / Position 1 VNI	51.45	3.018	10	24.144	3.226	10	16.7%	27.31 [24.57, 30.04]
Ari / Position 2 VI	30.2	1	3	9.7	1.5	3	16.9%	20.50 [18.46, 22.54]
Ari / Position 3 VI	24.2	1.2	3	14.7	1.5	3	16.9%	9.50 [7.33, 11.67]
Ari / Position 1 VI	14.5	1	3	7.6	0.9	3	17.0%	6.90 [5.38, 8.42]
Sidler / Position 2 VI	13.3	4.6	5	3.7	0.3	5	16.1%	9.60 [5.56, 13.64]
Total (95% CI)			**34**			**34**	**100.0%**	**14.30 [7.67, 20.92]**

Heterogeneity: Tau² = 66.51; Chi² = 231.53, df = 5 (P < 0.00001); I² = 98%

Test for overall effect: Z = 4.23 (P < 0.0001)



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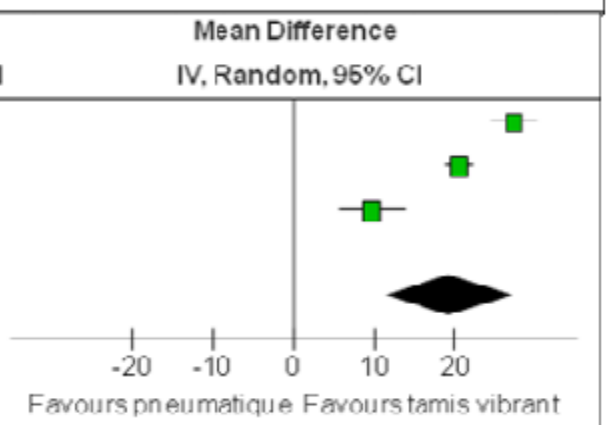
Ari / Position 2 VI	30.2	1	3	9.7	1	3	34.5%	20.50 [18.90, 22.10]
Sidler / Position 2 VI	13.3	4.6	5	3.7	0.3	5	32.0%	9.60 [5.56, 13.64]
Total (95% CI)			**18**			**18**	**100.0%**	**19.30 [11.55, 27.04]**

Heterogeneity: Tau² = 44.62; Chi² = 51.31, df = 2 (P < 0.00001); I² = 96%

Test for overall effect: Z = 4.88 (P < 0.00001)



Les résultats de cette revue ont montré qu'en ventilation mécanique, l'utilisation d'un nébuliseur à tamis vibrant permet d'augmenter significativement la dose émise par rapport à un nébuliseur pneumatique. Pour la ventilation mécanique invasive, ils montrent également que la position optimale du nébuliseur se situe sur le circuit inspiratoire 10 – 40 cm avant la pièce en Y. Pour la ventilation mécanique non-invasive, ils montrent que la position optimale du

nébuliseur se situe sur le circuit entre le patient et la valve expiratoire. Ces bénéfices sont explicables par l'avancée technologique de ces dernières années. Le nébuliseur à tamis vibrant a été spécialement conçu pour la nébulisation en ventilation mécanique, il permet principalement d'obtenir des particules de diamètre inférieur, et augmente de ce fait la dose émise.

Variables influençant la dose émise :

- Position du nébuliseur,
- Mode vent. et paramètres du ventilateur
- Type de médicament (taille des particules)
- Facteurs liés au patient (Capacité Vitale)
- Sévérité de la bronchopneumonie

Règles de Nébulisation

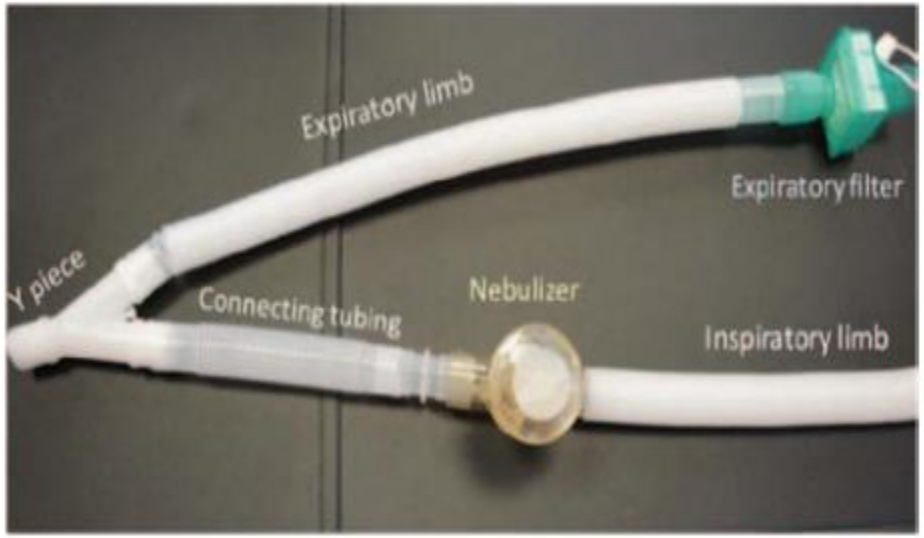
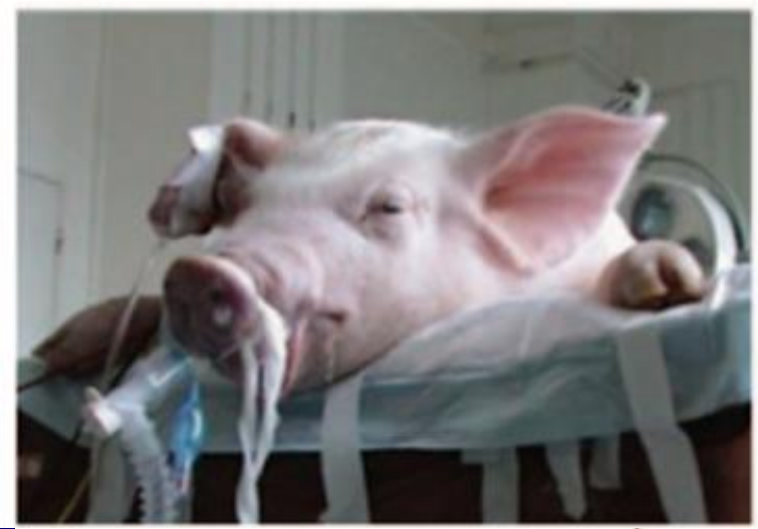
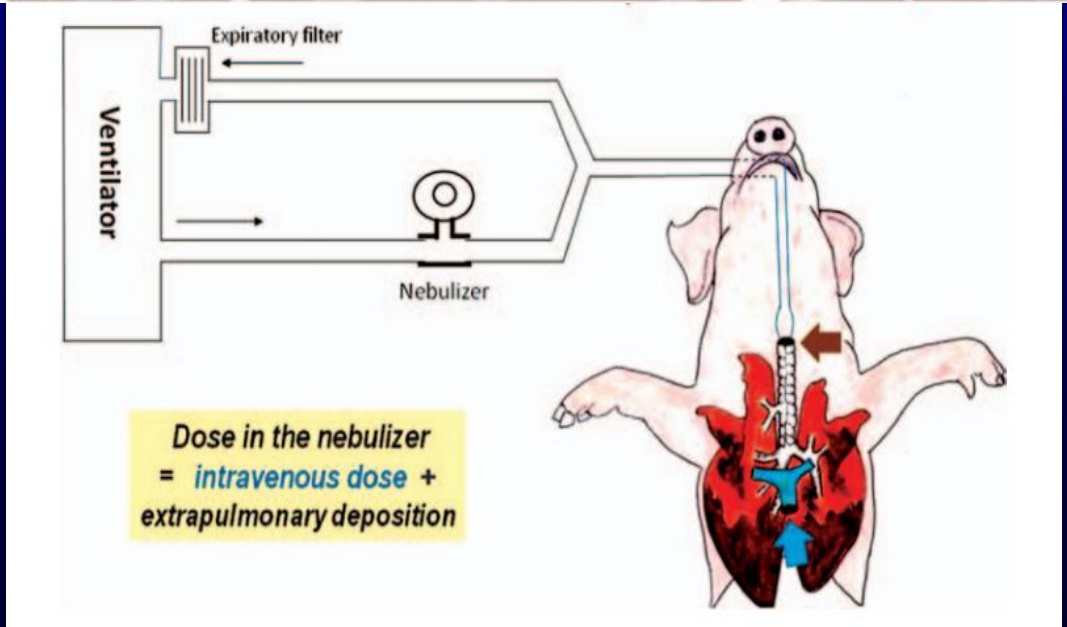


Fig. 5. Specific artificial airways recommended for nebulization of antibiotics. The Y piece is specifically designed for limiting impaction of aerosolized particles.

INHALED ATB IN VAP
Lessons from Experimental Studies

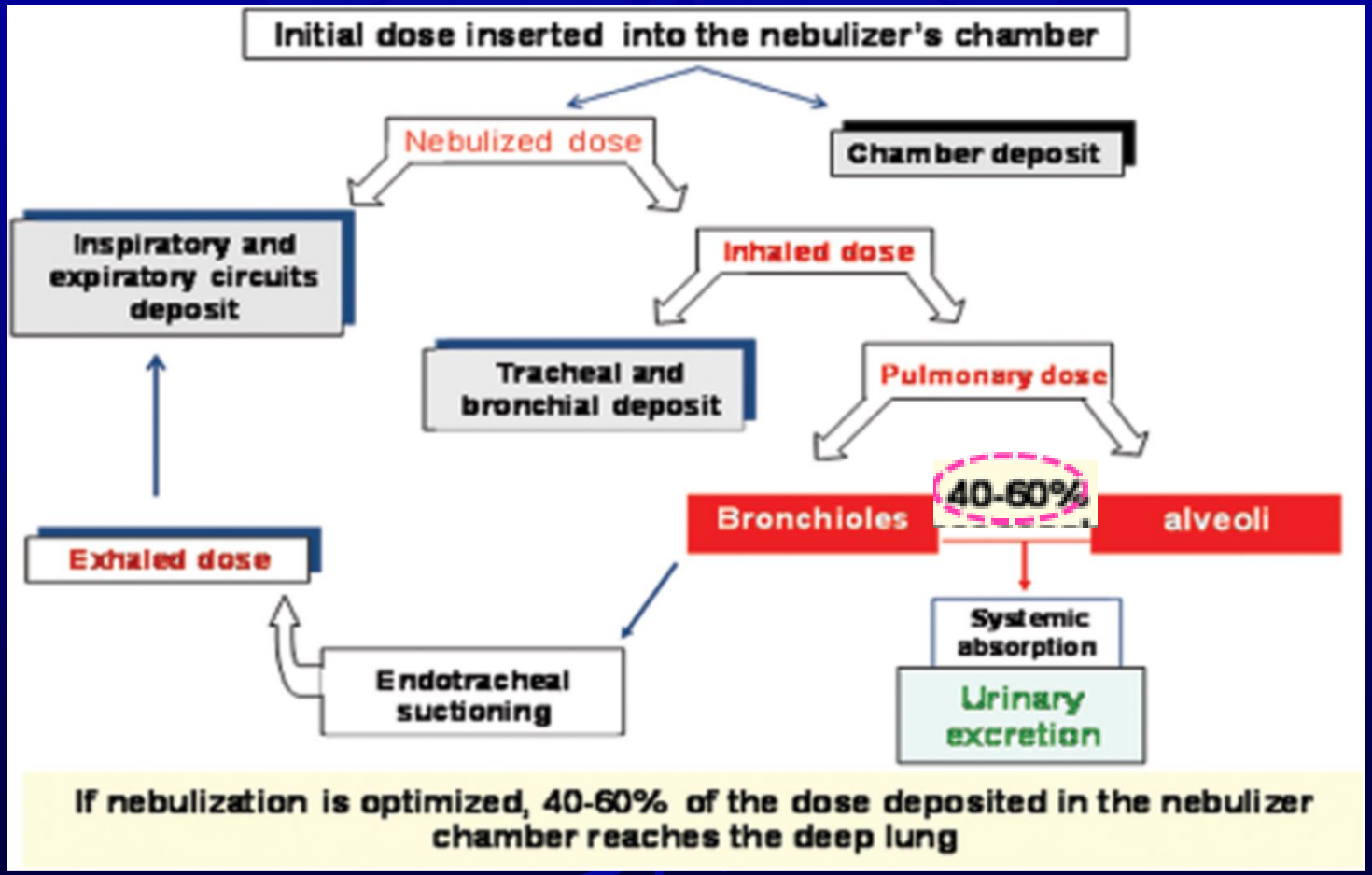




la concentration intra parenchymateuse d'ATB Neb >>> IV même dans les zones les moins aérées

ANESTHESIOLOGY
The Journal of the American Society of Anesthesiologists, Inc.

From: Aerosolized Antibiotics for Ventilator-associated Pneumonia:Lessons from Experimental Studies
Anesthesiology. 2012;117(6):1364-1380. doi:10.1097/ALN.0b013e3182755d7a



Mechanisms by which the dose of antibiotic inserted into the nebulizer differs from the dose delivered to the infected lung parenchyma.

Anesthesiology 2005; 102:995–1000

Intravenous versus Nebulized Ceftazidime in Ventilated Piglets with and without Experimental Bronchopneumonia

Comparative Effects of Helium and Nitrogen

Marc Tonnellier, M.D.,‡ Fabio Ferrari, M.D.,† Ivan Goldstein, M.D., Ph.D.,‡ Alfonso Sartorius, M.D.,§ Charles-Hugo Marquette, M.D., Ph.D.,‖ Jean-Jacques Rouby, M.D., Ph.D.#

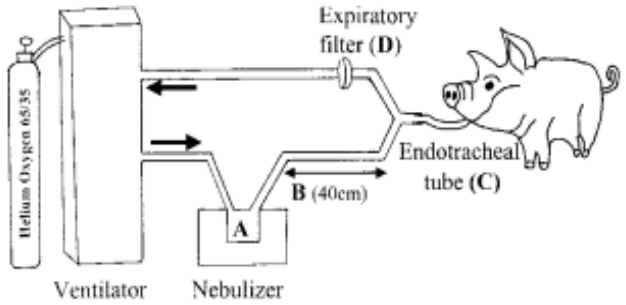


Fig. 1. Diagram showing the experimental setting. The ultrasonic nebulizer is positioned 40 cm before the Y piece connecting inspiratory and expiratory limbs to the proximal tip of the endotracheal tube. An expiratory filter is inserted on the expiratory limb, just after the Y piece. Extrapulmonary deposition is defined as the amount of ceftazidime trapped in *A*, *B*, *C*, and *D* after nebulization.

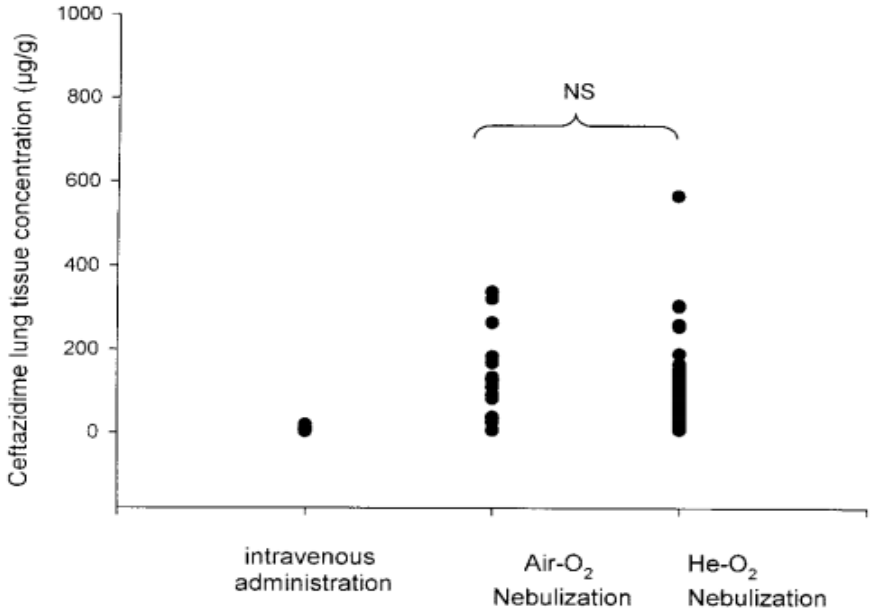


Fig. 3. Lung tissue concentrations of ceftazidime obtained in 15 piglets with experimental bronchopneumonia. Fifteen minutes after intravenous administration of 33 mg/kg ceftazidime (n = 5) or administration of 1 g ceftazidime by an ultrasonic nebulizer, using 65%/35% nitrogen–oxygen (n = 5) or helium–oxygen (n = 5) as the operating gas of the ventilator, animals were

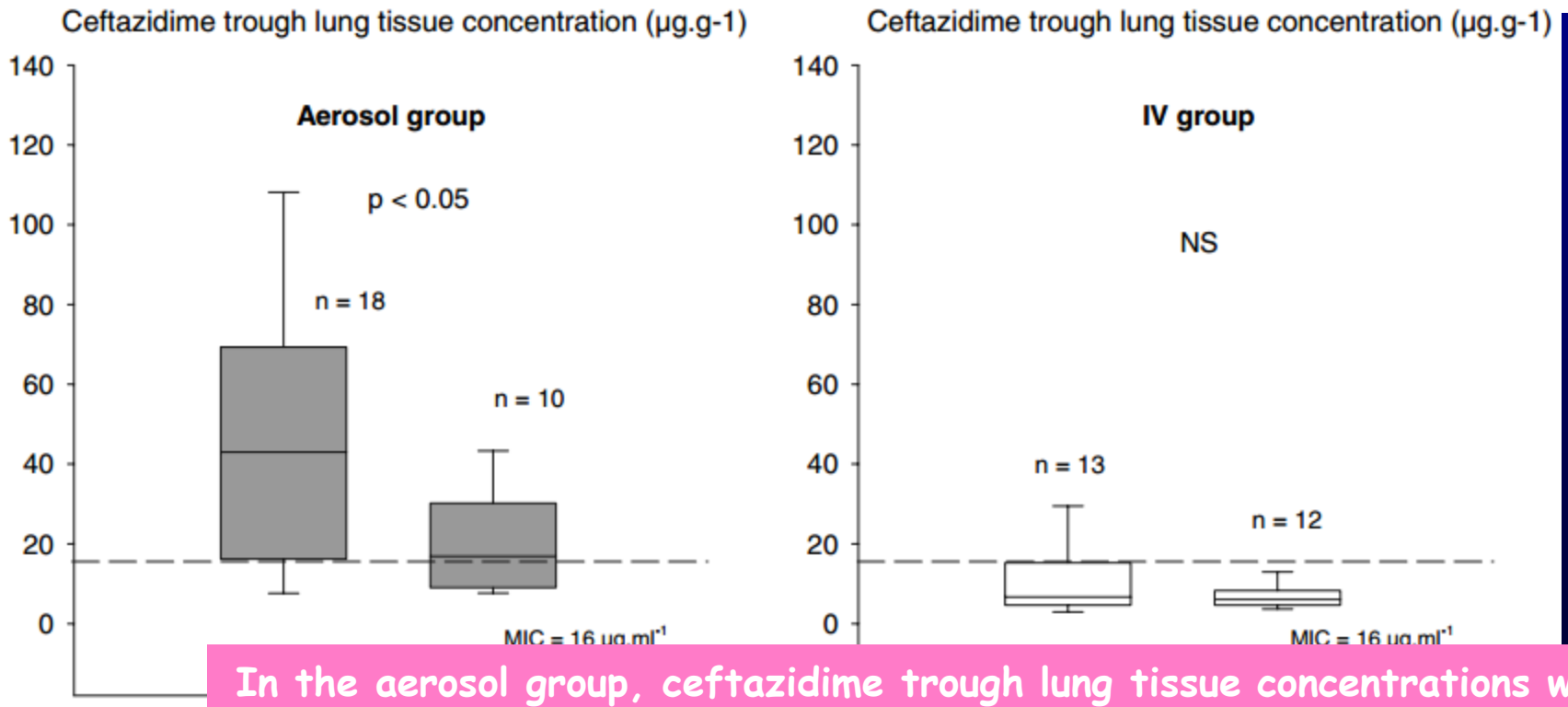
CC: Nebulization of ceftazidime induced a 5- to 30-fold increase in lung tissue concentrations as compared with intravenous administration

Intensive Care Med (2009) 35:1792–1800
DOI 10.1007/s00134-009-1605-2

EXPERIMENTAL

Fabio Ferrari
Qin Lu
Cassio Girardi
Olivier Petitjean
Charles-Hugo Marquette
Frederic Wallet
Jean-Jacques Rouby
the Experimental ICU Study Group

Nebulized ceftazidime in experimental pneumonia caused by partially resistant *Pseudomonas aeruginosa*



In the aerosol group, ceftazidime trough lung tissue concentrations were significantly greater in lung segments with mild pneumonia ($p<0.05$)

Intensive Care Med (2009) 35:1792–1800
DOI 10.1007/s00134-009-1605-2

EXPERIMENTAL

Fabio Ferrari
Qin Lu
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Nebulized ceftazidime in experimental

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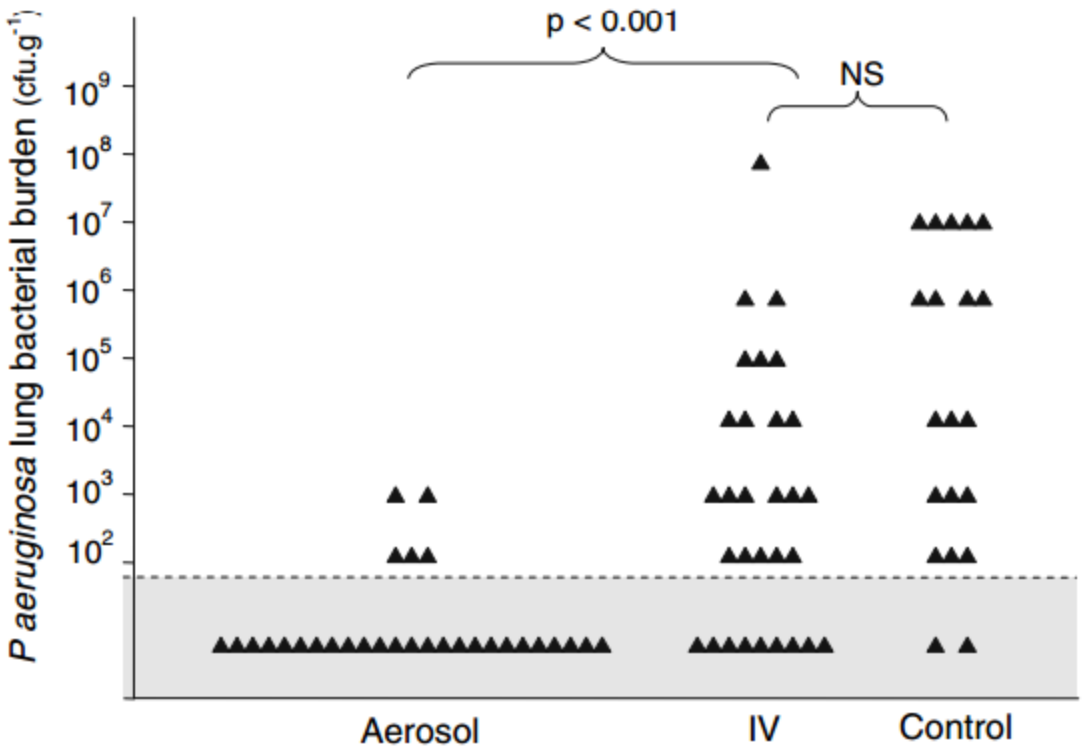

Lung bacterial burden **was significantly lower** in the aerosol group compared to the intravenous and control groups. The difference was not statistically significant between intravenous and control groups.

Intensive Care Med (2009) 35:1792–1800
DOI 10.1007/s00134-009-1605-2

EXPERIMENTAL

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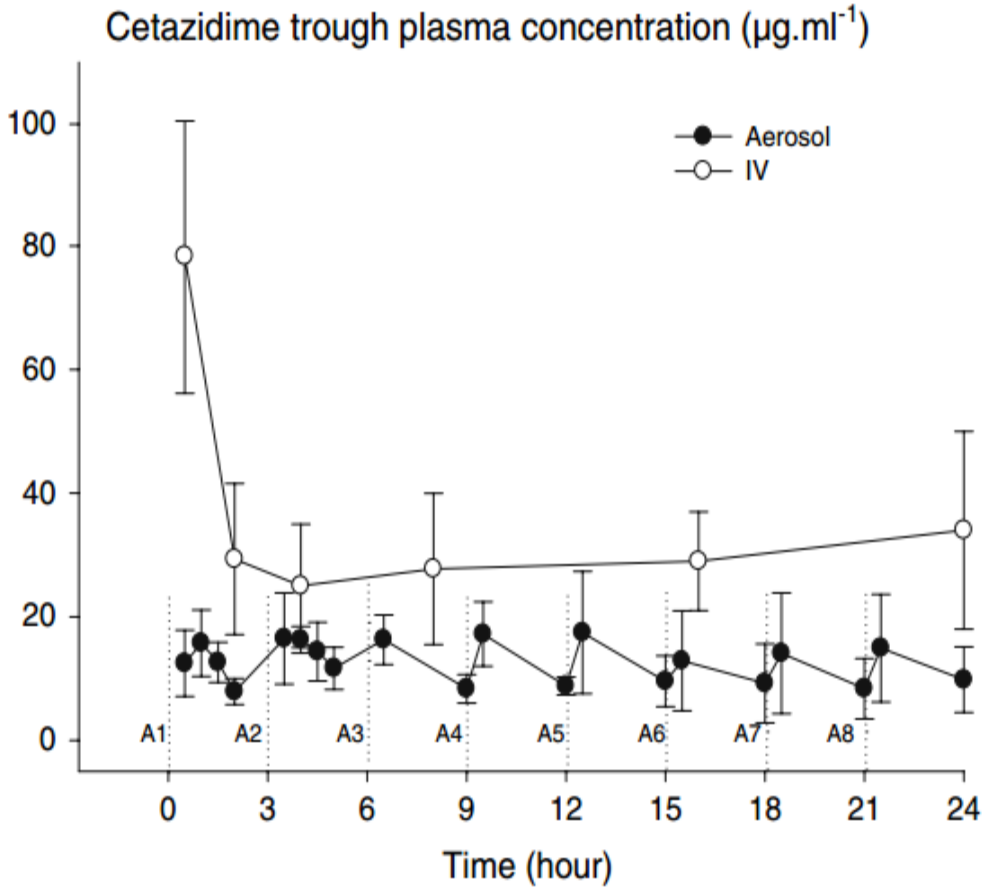
Nebulized ceftazidime in experimental pneumonia caused by partially resistant *Pseudomonas aeruginosa*



- Peak and trough plasma concentrations were similar after each successive aerosol, suggesting the lack of ceftazidime accumulation.
- In the aerosol group, mean peak plasma concentrations were significantly lower than steady-state plasma concentrations in IV group

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 166 2002

Lung Deposition and Efficiency of Nebulized Amikacin during *Escherichia coli* Pneumonia in Ventilated Piglets

Ivan Goldstein, Frederic Wallet, Armelle Nicolas-Robin, Fabio Ferrari, Charles-Hugo Marquette, Jean-Jacques Rouby, and the Experimental Intensive Care Unit Study Group

Réanimation Chirurgicale Pierre Viars, Department of Anesthesiology, Pitié-Salpêtrière Hospital, University of Paris VI, Paris; and Department of Bacteriology, DHURE and INSERM U 416, University of Medicine, Lille, France

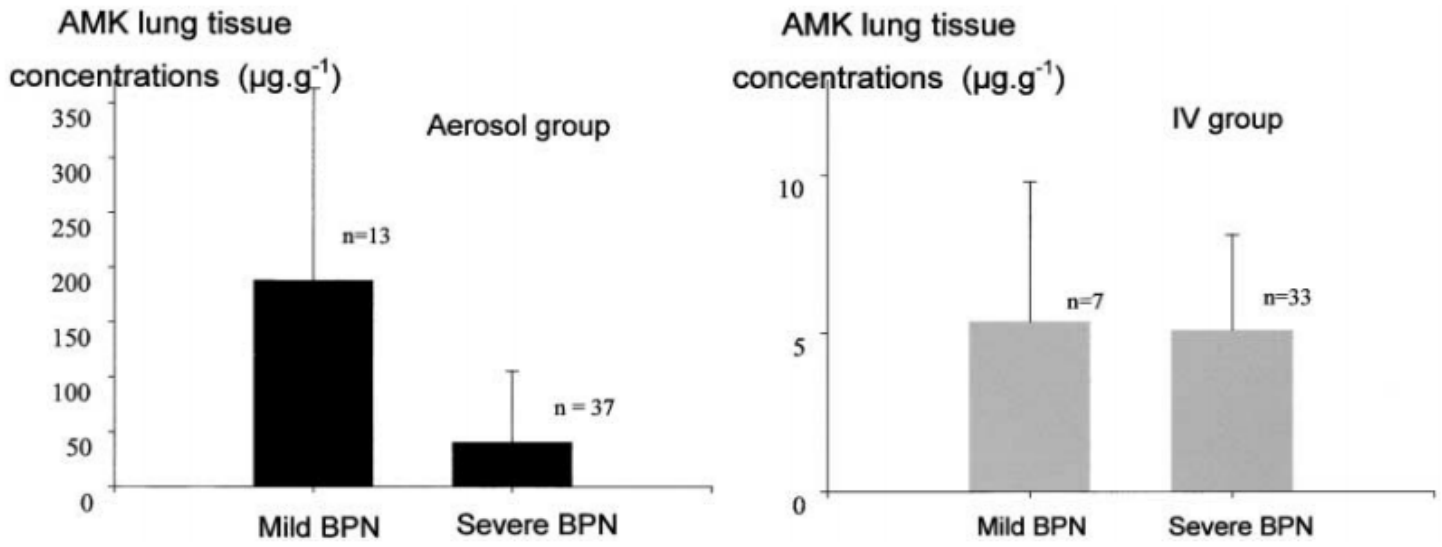
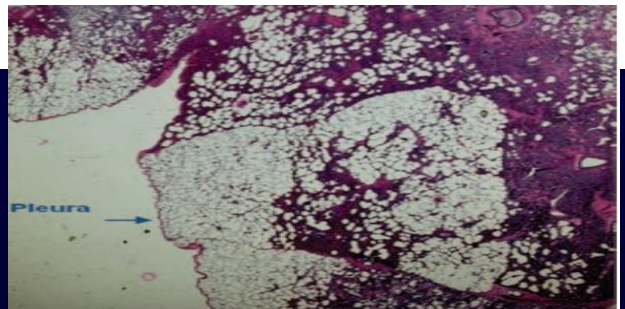


Figure 3. AMK lung tissue concentrations according to the histologic grade of bronchopneumonia (BPN) characterizing lung segments in the aerosol (*left panel*) and intravenous (IV) groups (*right panel*); *n* indicates the number of lung segments belonging to each histological category in each group. In the aerosol group, AMK lung tissue concentrations were greater in lung segments with mild BPN than in lung segments with severe BPN (*$p < 0.05$).



AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 166 2002

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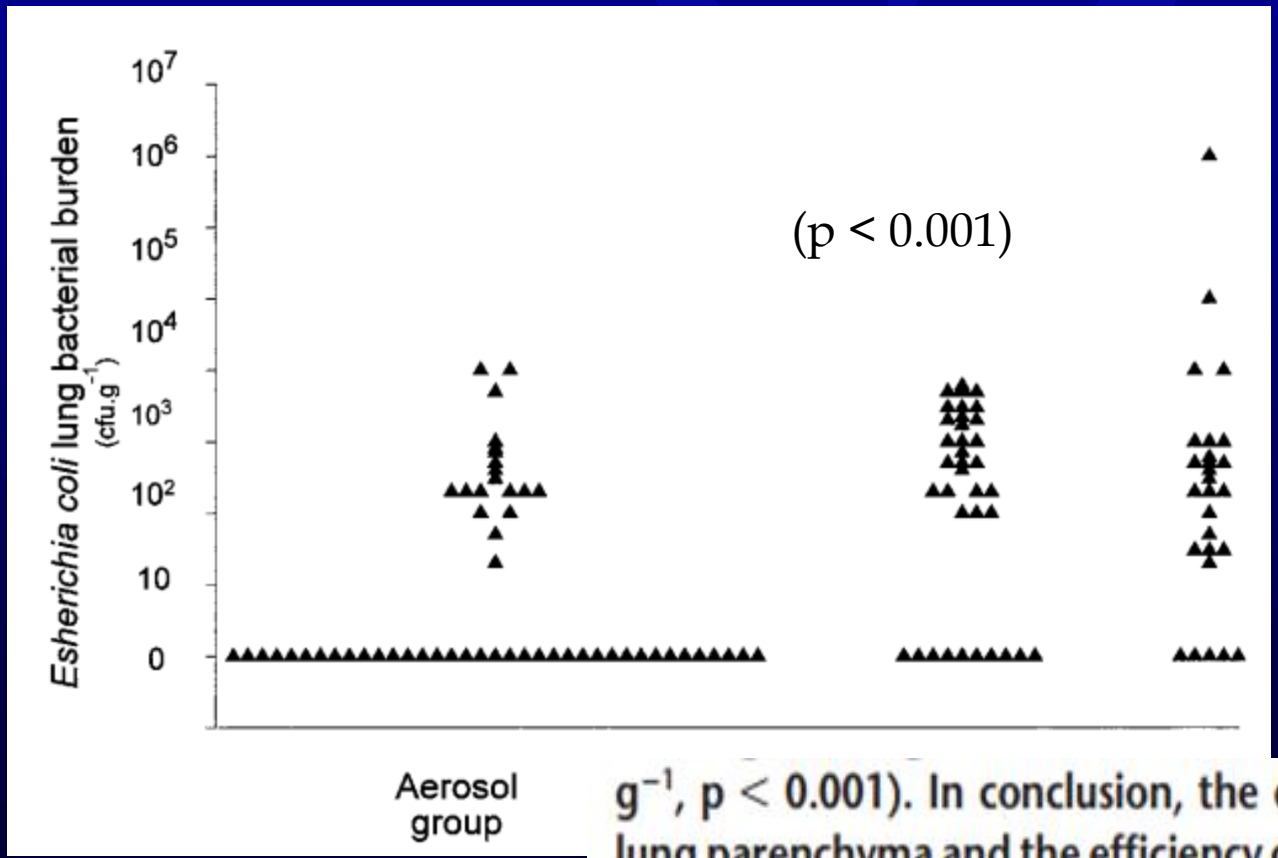

($p < 0.001$)

g^{-1}, $p < 0.001$). In conclusion, the deposition of AMK in infected lung parenchyma and the efficiency of bacterial killing were greater after nebulization than after intravenous administration.

Intensive Care Med (2010) 36:1147–1155
DOI 10.1007/s00134-010-1879-4

ORIGINAL

Qin Lu
Cassio Girardi
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Gilles Le Naour
Charles-Hugo Marquette
Jean-Jacques Rouby

Nebulized and intravenous colistin in experimental pneumonia caused by *Pseudomonas aeruginosa*

The aim of this study is **to compare** lung tissue deposition and antibacterial efficiency between **nebulized and iv** administration of **colistin** in piglets with pneumonia caused by **P. aeruginosa**

Intensive Care Med (2010) 36:1147–1155
DOI 10.1007/s00134-010-1879-4

ORIGINAL

Qin Lu
Cassio Girardi
Mao Zhang
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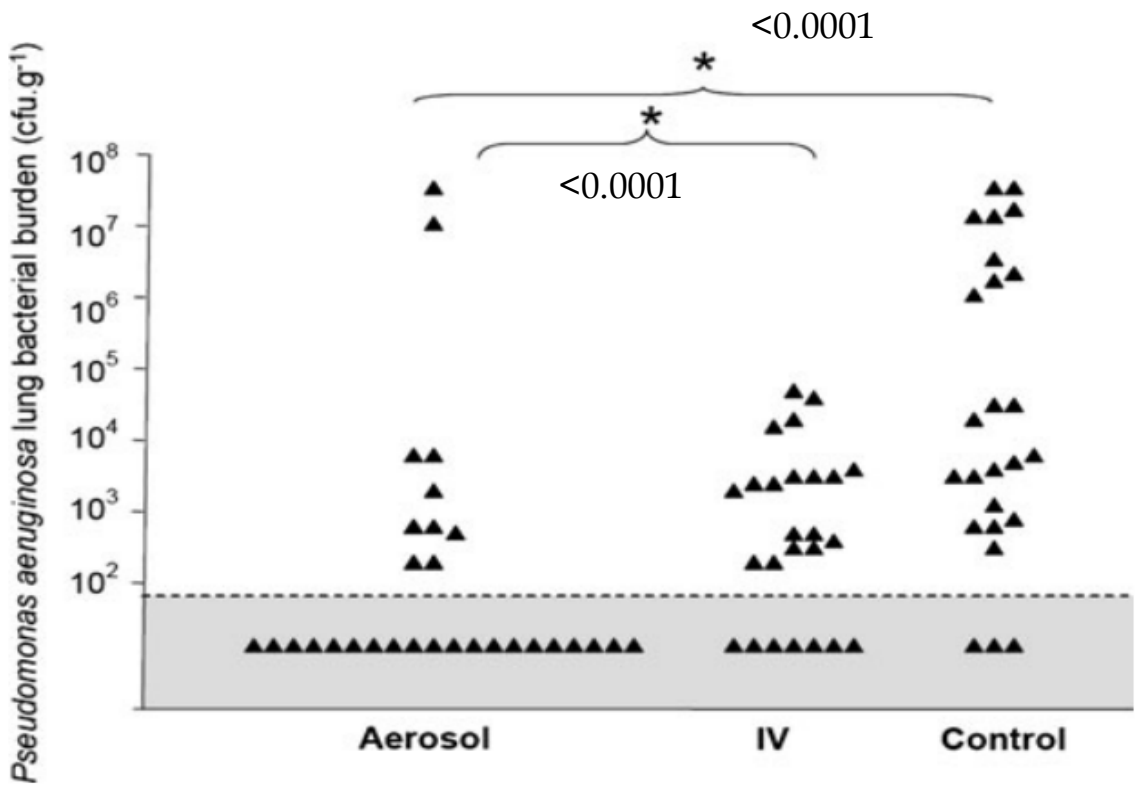
Nebulized and intravenous colistin in experimental pneumonia caused



Lung bacterial burden of Pseudomonas aeruginosa after 24 h of colistin administration. Lung segments (triangles) were sampled 1 h after the third aerosol in the aerosol group and after the fourth infusion in the intravenous group (IV) and 48 h after the bacterial inoculation in the untreated control group.

INHALED ATB IN VAP
Lessons from Experimental Studies

- Résultats encourageants

↓

- Fort rationnel
- Études/essais cliniques: évaluation des ATB inhalés dans le ttt des PAV

Journal of the Royal Society of Medicine

Inhaled antibiotics in cystic fibrosis: what's new?

J R Soc Med 2012: **105 (S2)**: S19–S24. DOI 10.1258/jrsm.2012.12s004

Aztreonam lysine (AZLI)

The pharmaceutical company, Gilead, developed AZLI which was approved in the US and UK in 2010 for use as a nebulized antibiotic in CF patients with *Pseudomonas aeruginosa*. It has been developed for use specifically with it's own nebulizer, the Altera, which is based on the

Tobramycin Inhalation Powder (TIP).

In summary, TIP is now licensed and available for children and adults with CF, and offers an alternative delivery method to TIS which is portable, more convenient than a nebulizer and not dependant on an electrical power source. Some patients will prefer this though should be warned of the possibility of cough, dysphonia and taste disturbance after inhalation. The UK

D'autres ATB à inclure dans l'arsenal ttt de la mucoviscidose?

Liposomal amikacin – Arikace

In phase III clinical trials as an anti-*Pseudomonas* antibiotic under development with Insmed. In the US, clinical trials are on hold following a request by FDA for further animal studies to be performed to investigate toxicity. Unlicensed and no clear launch date available.

Liposomal ciprofloxacin

Undergoing phase II clinical trials in development with Aradigm. Trials are focusing on once daily usage as an anti-*Pseudomonas* antibiotic in CF and non-CF bronchiectasis. No UK launch date.

Levofloxacin – Aeroquin

Another quinolone antibiotic undergoing phase III clinical trials with Mpex. A multicentre multinational trial in 267 stable CF patients over 12 years of age with *Pseudomonas aeruginosa* infection is due to complete during 2012.

Colistin – Colobreathe

Dry powder formulation of colistin (already in use as an intravenous and nebulized antibiotic) developed by Forest. Phase III studies have been performed but not yet published so Colobreathe is currently unlicensed and with a launch date yet to be confirmed.

Fosfomycin/tobramycin combination

Phase II safety and efficacy trials are underway in the United States in adult patients with chronic *Pseudomonas aeruginosa* infection and preliminary data have been released but not yet published.

Russell *et al. BMC Pulmonary Medicine* (2016) 16:40
DOI 10.1186/s12890-016-0202-8

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

The use of inhaled antibiotic therapy in the treatment of ventilator-associated pneumonia and tracheobronchitis: a systematic review

Christopher J. Russell[1,2*], Mark S. Shiroishi[3], Elizabeth Siantz[6], Brian W. Wu[4] and Cecilia M. Patino[5]

unclear. Our objective was to conduct a systematic review of the efficacy of aerosolized antibiotics in the treatment of ventilator-associated pneumonia (VAP) and tracheobronchitis (VAT), using the Cochrane Collaboration guidelines.

Russell *et al. BMC Pulmonary Med*
DOI 10.1186/s12890-016-0202-8

RESEARCH ART

The use of i treatment c pneumonia systematic r

Christopher J. Russell[1,2*]

Inclusion criteria

Included studies met all of the follo

1. Patients: Study population was ventilated patients diagnosed wi
2. Intervention: Use of inhaled ant of VAP or VAT compared to O intravenous antibiotics
3. Reported outcomes of a randon and
4. Outcome: Reported on some m clinical cure as an outcome (e.g infection score [CPIS])

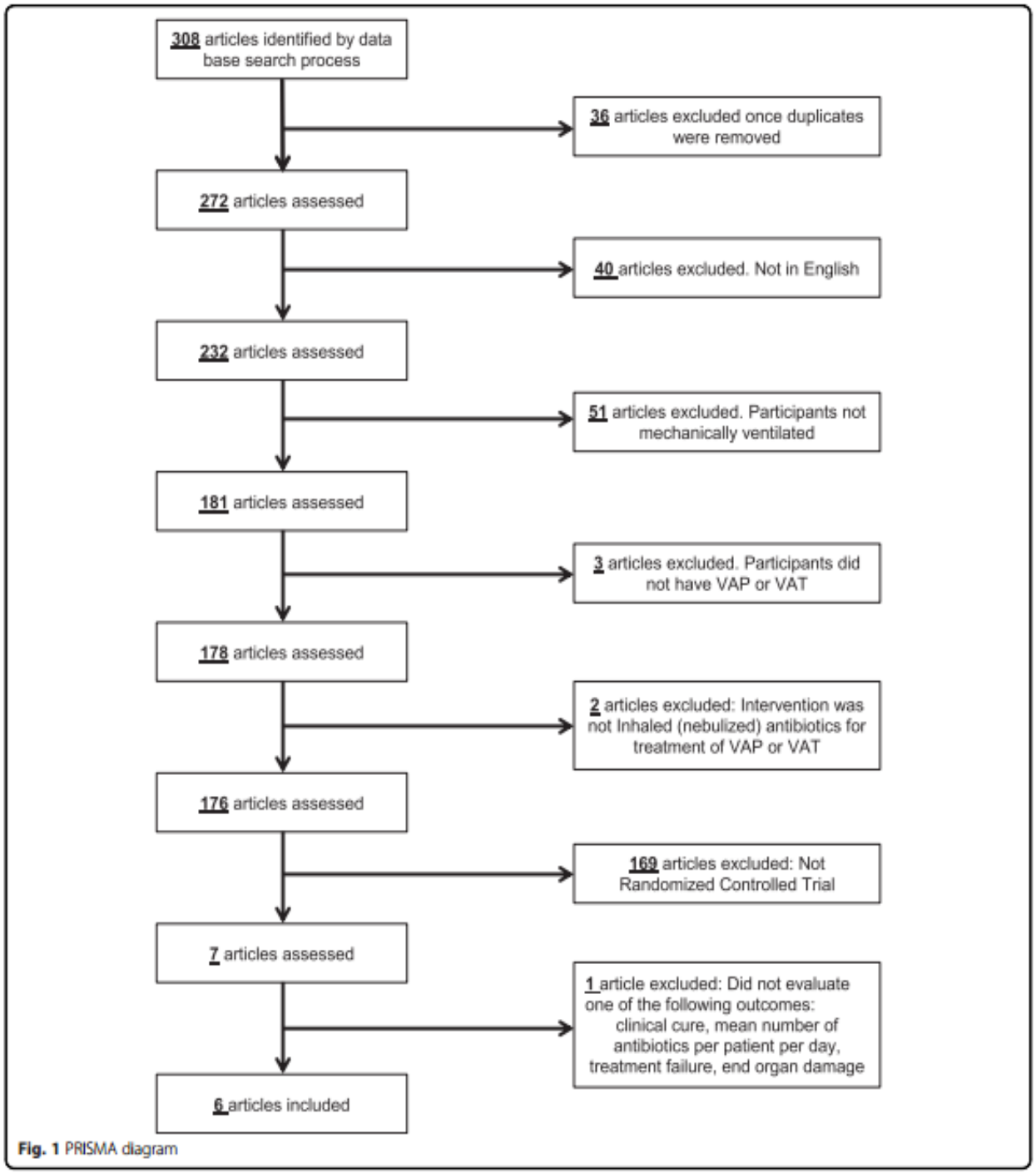


Fig. 1 PRISMA diagram

Russell *et al. BMC Pulmonary Medicine* (2016) 16:40
DOI 10.1186/s12890-016-0202-8

BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

Table 1 Study Characteristics, Quality and Results, in Chronological Order

Author and year	Study Participants (age, in years)	Description of intervention	Study period	Length of follow up	Primary Outcome (successful treatment)	Results
Hallal, et al, 2007 [9]	*N* = 10 Age: 23–72 (Mean age: AA 52.6, IV 53.6)	Inhaled tobramycin or IV tobramycin AND IV β-lactam	7 months	28 days	Resolution of VAP	100 % of AA vs. 60 % of IV patients had clinical resolution of VAP. No p value reported.
Palmer et al, 2008 [12]	*N* = 43 Age: 19–92 (Mean age: AA 62.3, placebo 62.7)	AA or saline placebo AND systemic antibiotics (per treating MD) was given for 14 days or until extubation	12 months	28 days	Centers for Disease Control National Nosocomial Infection Survey diagnosis of ventilator associated pneumonia (VAP) and clinical pulmonary infection Score (CPIS)	AA group had reduced signs of respiratory infection [Centers for Disease Control National Nosocomial Infection Survey and VAP (73.6 % to 35.7 % vs. placebo: 75 % to 78.6 %) and reduction in clinical pulmonary infection score (−1.42 vs. placebo: + 0.04), (both p ≤ .05).
Rattanaumpawan et al, 2010 [14]	*N* = 100 (Mean age: AA 70.2, placebo 66.2)	Nebulized colistimethate sodium or nebulized sterile normal saline AND systemic antibiotics per treating MD	38 months	28 days	Favorable clinical outcome	Favorable clinical outcome was 51.0 % in the AA group and 53.1 % in the placebo group ($p = 0.84$). Significant increase in favorable microbiological outcome in AA vs. placebo group (60.9 vs. 38.2 %; $p = 0.03$)
Lu et al, 2011 [10]	*N* = 40 patients Ages 43–77 (Mean age: AA 58, IV 60)	Nebulized ceftazidime and amikacin OR IV ceftazidime and amikacin/ciprofloxacin.	36 month	28 days	Successful treatment	AA and IV groups performed similar in terms of successful treatment (70 vs. 55 %; $p = 0.33$).
Niederman et al, 2012 [11]	*N* = 69 (Mean age: AA q12h 56.1, AA q24h 62.8, or placebo 62.0)	Inhaled amikacin (BAY41-6551) q12h, q24h, or placebo q12h for 7–14 days, plus standard IV antibiotics	13 months	31 days	Clinical cure (secondary study outcome)	Clinical cure achieved in 93.8 % (AA q12h), 75 % (AA q24h) and 87.5 % (placebo; $p = 0.467$).
Palmer et al, 2014 [13]	*N* = 43 (Mean age AA 57.5, placebo 60.6)	AA or saline placebo AND systemic antibiotics (per treating MD) was given for 14 days or until extubation	Does not state	14 days	Clinical Pulmonary Infection Score (CPIS)	CPIS score in AA significantly reduced when compared to placebo (Mean ± SE AA: 9.3 ± 2.7 to 5.3 ± 2.6 vs. placebo: 8.0 ± 23 to 8.6 ± 2.10; $p = 0.0008$)

Abbreviations: *AA* aerosolized antibiotics, *CPIS* Clinical Pulmonary Infection Score; *SEM* standard error of the mean, *VAP* ventilator-associated pneumonia

Garnacho-Montero *et al. BMC Infectious Diseases* 2014, **14**:135
http://www.biomedcentral.com/1471-2334/14/135

BMC Infectious Diseases

REVIEW Open Access

How to treat VAP due to MDR pathogens in ICU patients

José Garnacho-Montero[1,2,3*], Yael Corcia-Palomo[1], Rosario Amaya-Villar[1,3] and Luis Martin-Villen[1]

Nebulized antibiotics

The administration of nebulized antibiotics has been proposed to provide high levels of the drug in the lung and to reduce the systemic toxicity associated with intravenous antibiotics. The concentration in the respiratory secretion of the nebulized antibiotic may be 20 to 100 fold greater than the *in-vitro* MIC of the organisms being treated [60]. Large randomized trials are needed to define the impact on clinical outcomes of nebulized antibiotics as adjunctive therapy in MDR-VAP.

Colistine:

- Actif sur les agents pathogènes à Gram négatif multirésistants (*P. aeruginosa ou A. baumannii*)
- Toxicité systémique par voie IV

- Intérêt d'aérosolthérapie /PAVM?

	N	Pathogènes	Eradication du pathogène	Mortalité
Kwa 2005	21	*P. aeruginosa* *A. baumannii*	86%	46.7%
Berlana 2005	70	*P. aeruginosa* *A. baumannii*	92%	18%
Michalopoulos 2008	80	*P. aeruginosa* *A. baumannii* *K. pneumoniae*	83%	25%

Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant Gram-negative bacteria: A prospective study ☆

Argyris Michalopoulos[a,*], Dimitrios Fotakis[a], Simona Virtzili[a], Christodoulos Vletsas[a], Sylvia Raftopoulou[a], Zefi Mastora[a], Matthew E. Falagas[b,c]

Respir Med 2009

→ Prospectif, observationnel
60 pts avec coli inhalée + ATB IV chez 57 pts
Guérison 83 %

Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study

I. P. Korbila[1], A. Michalopoulos[1,2], P. I. Rafailidis[1,3], D. Nikita[4], G. Samonis[5] and M. E. Falagas[1,3,6]

CMI 2010

→ Rétrospectif
- 78 pts coli IV + inhalée
- 43 pts coli IV seule

Coli inhalée : Facteur indépendant de guérison
Pas ≠ de mortalité

International Journal of Antimicrobial Agents 44 (2014) 477–485

Contents lists available at ScienceDirect

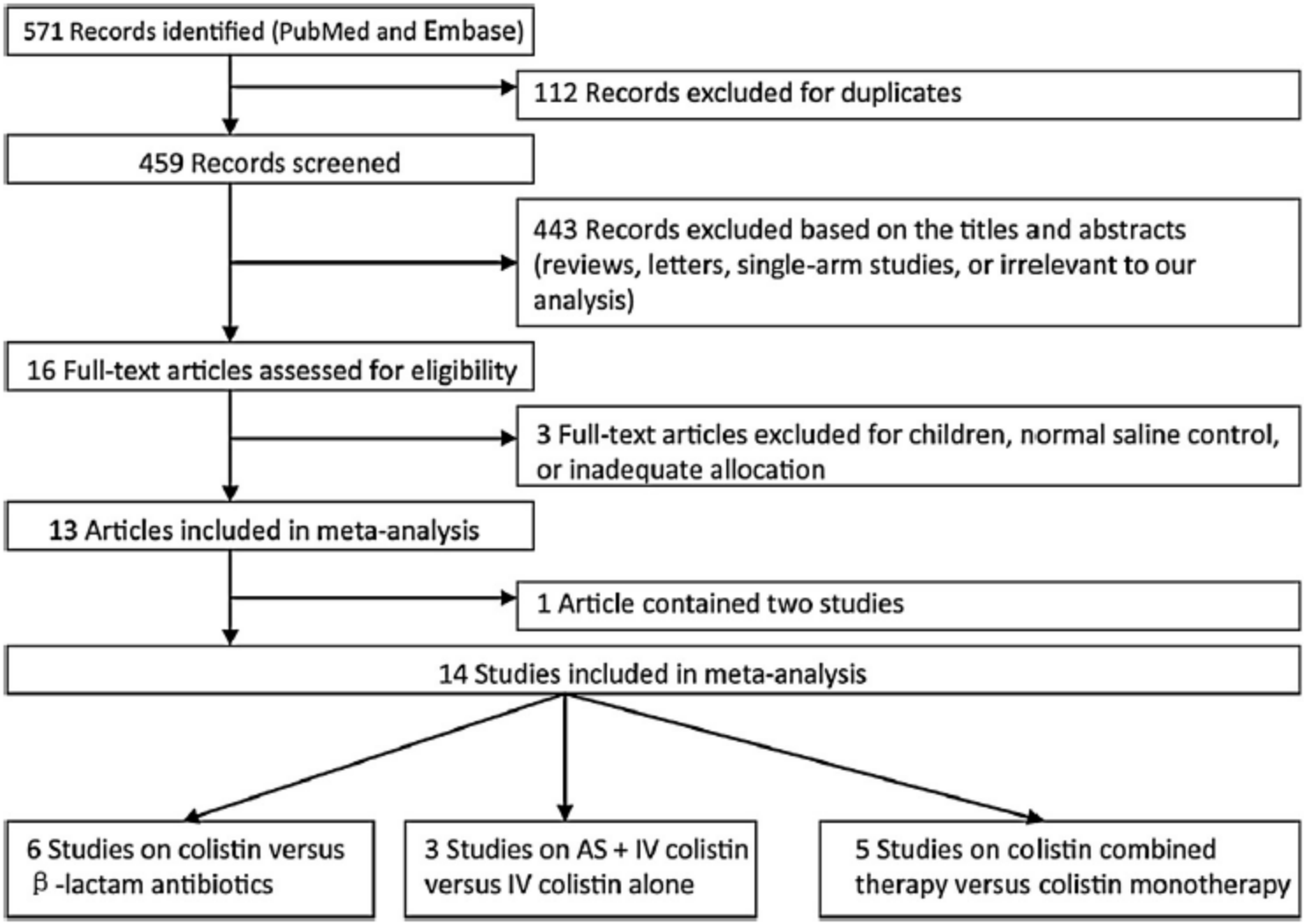


Fig. 1. Flow diagram of the selection process of the included studies. AS, aerosolised; IV, intravenous.

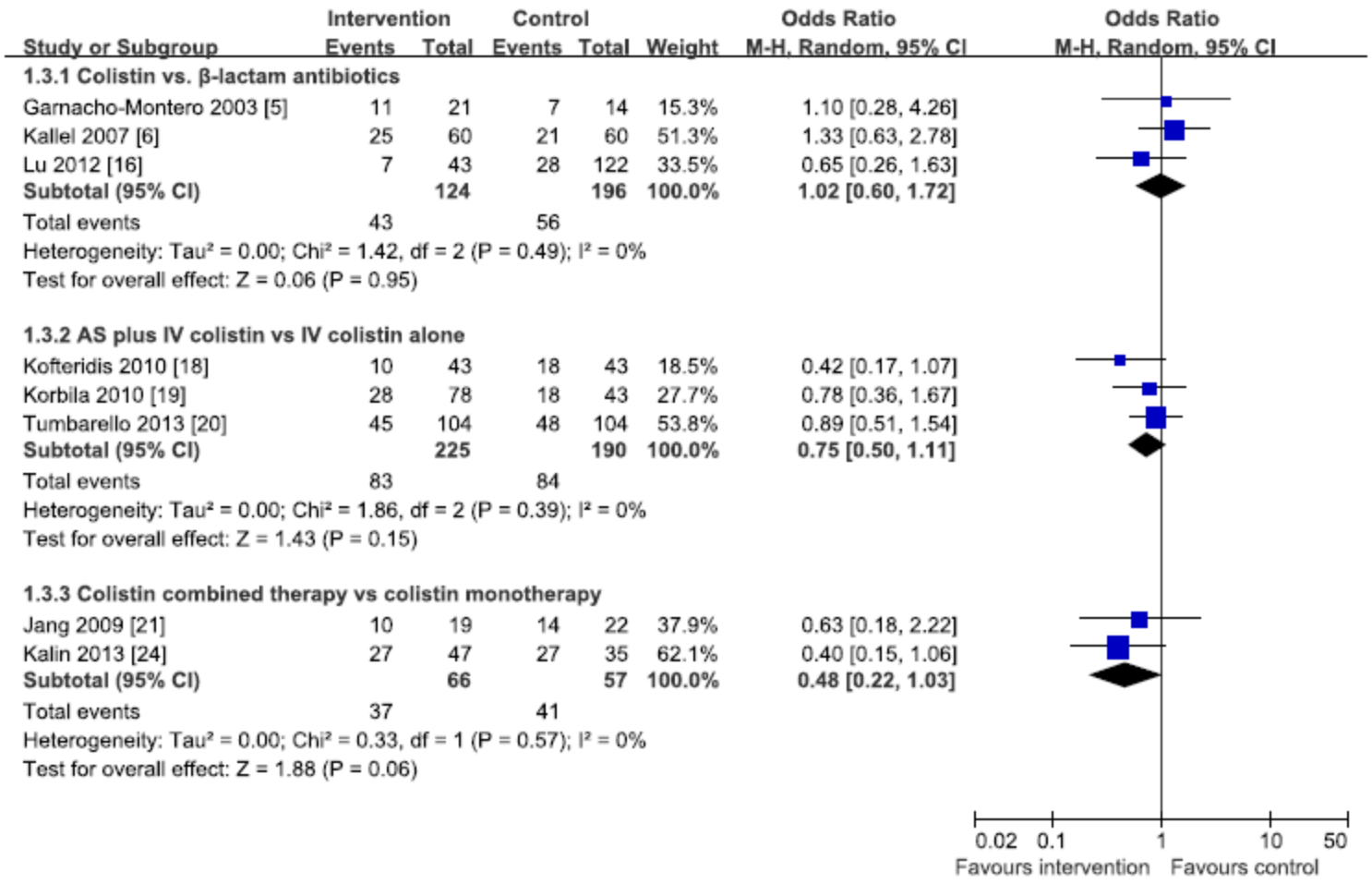


Fig. 4. Forest plot depicting intensive care unit mortality. AS, aerosolised; IV, intravenous.

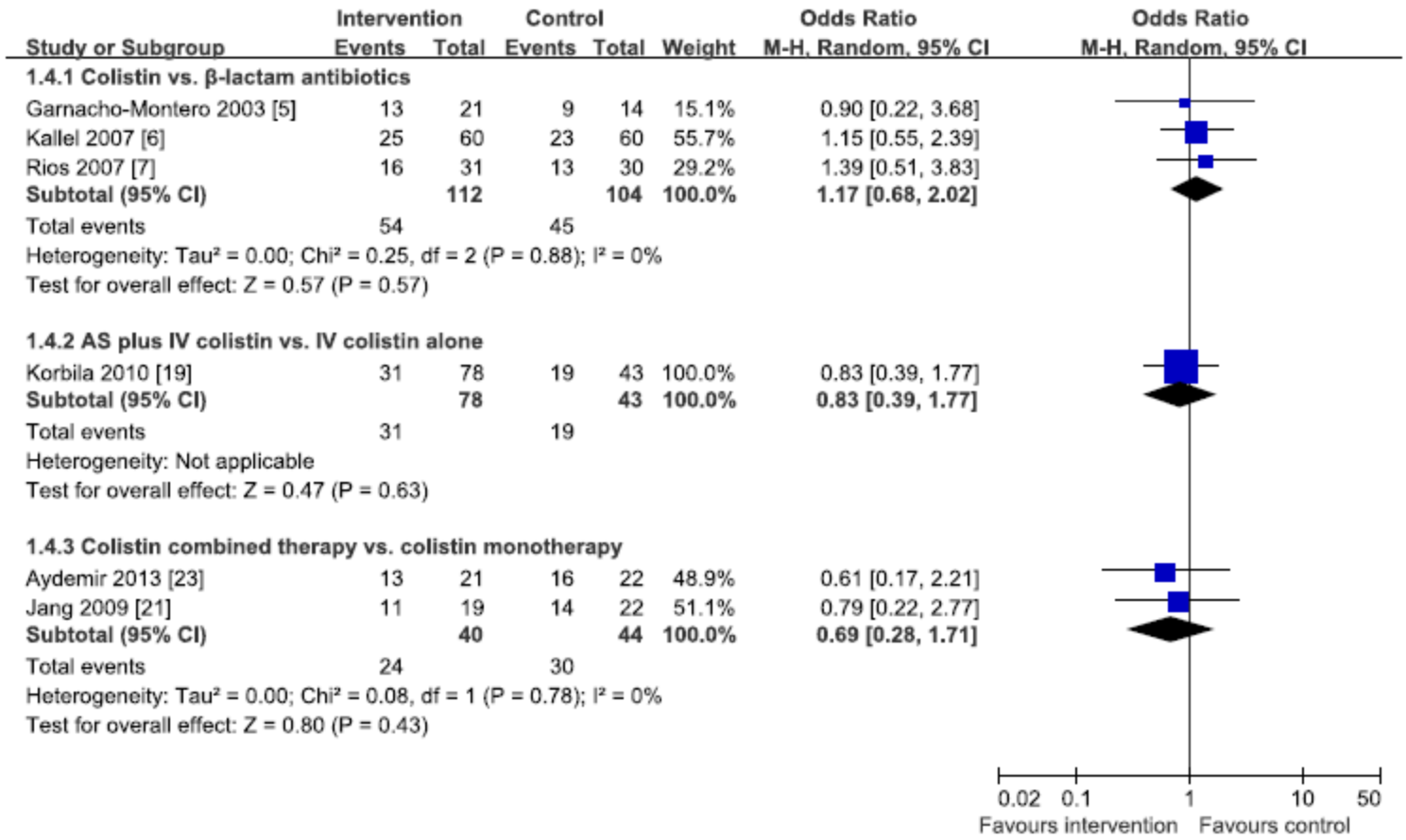


Fig. 5. Forest plot depicting hospital mortality. AS, aerosolised; IV, intravenous.

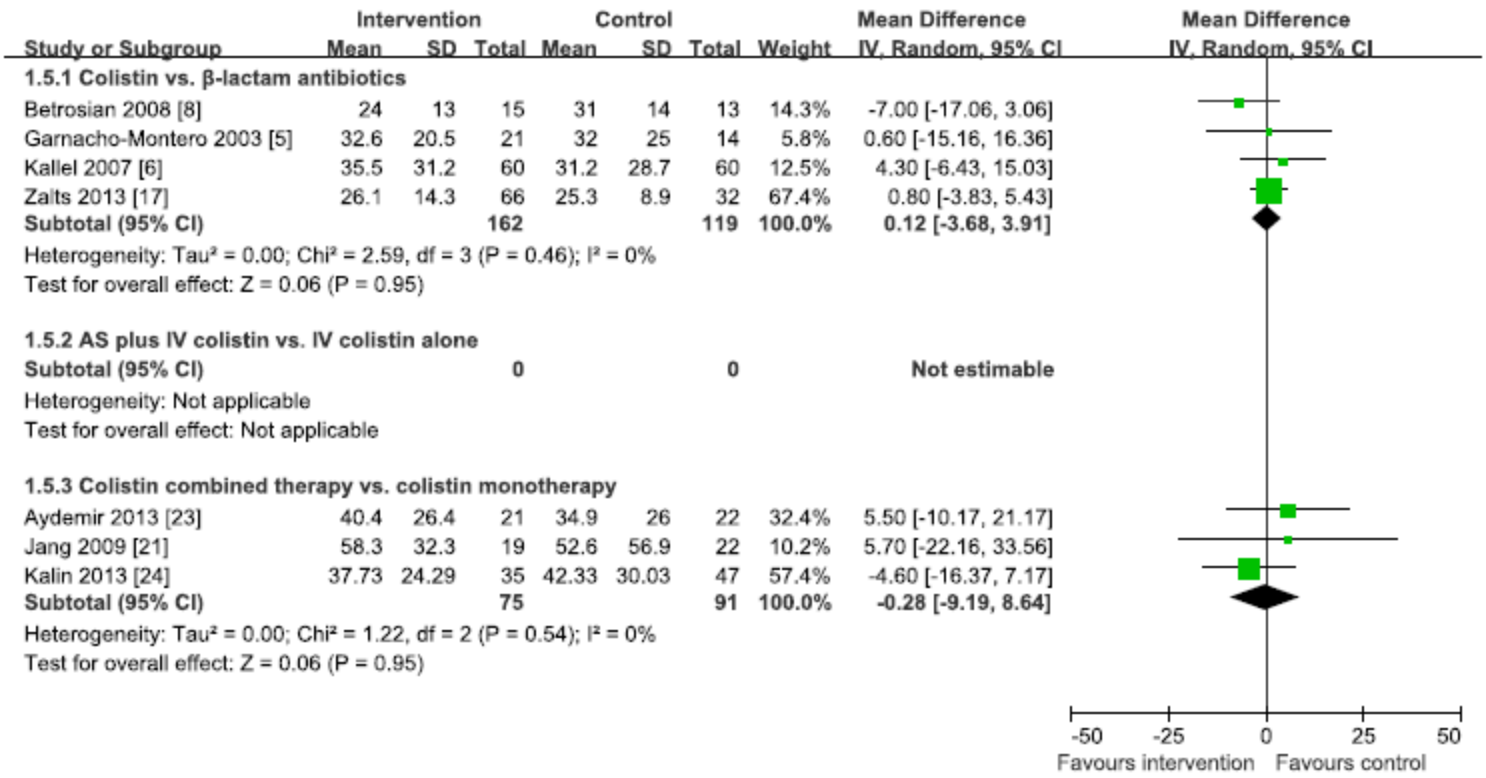


Fig. 6. Forest plot depicting the length of intensive care unit stay. AS, aerosolised; IV, intravenous.

Abdellatif *et al. Ann. Intensive Care* (2016) 6:26
DOI 10.1186/s13613-016-0127-7

Annals of Intensive Care

RESEARCH Open Access

Efficacy and toxicity of aerosolised colistin in ventilator-associated pneumonia: a prospective, randomised trial

Sami Abdellatif, Ahlem Trifi*, Foued Daly, Khaoula Mahjoub, Rochdi Nasri and Salah Ben Lakhal

Trial registration ClinicalTrials.gov Identifier: NCT02683603

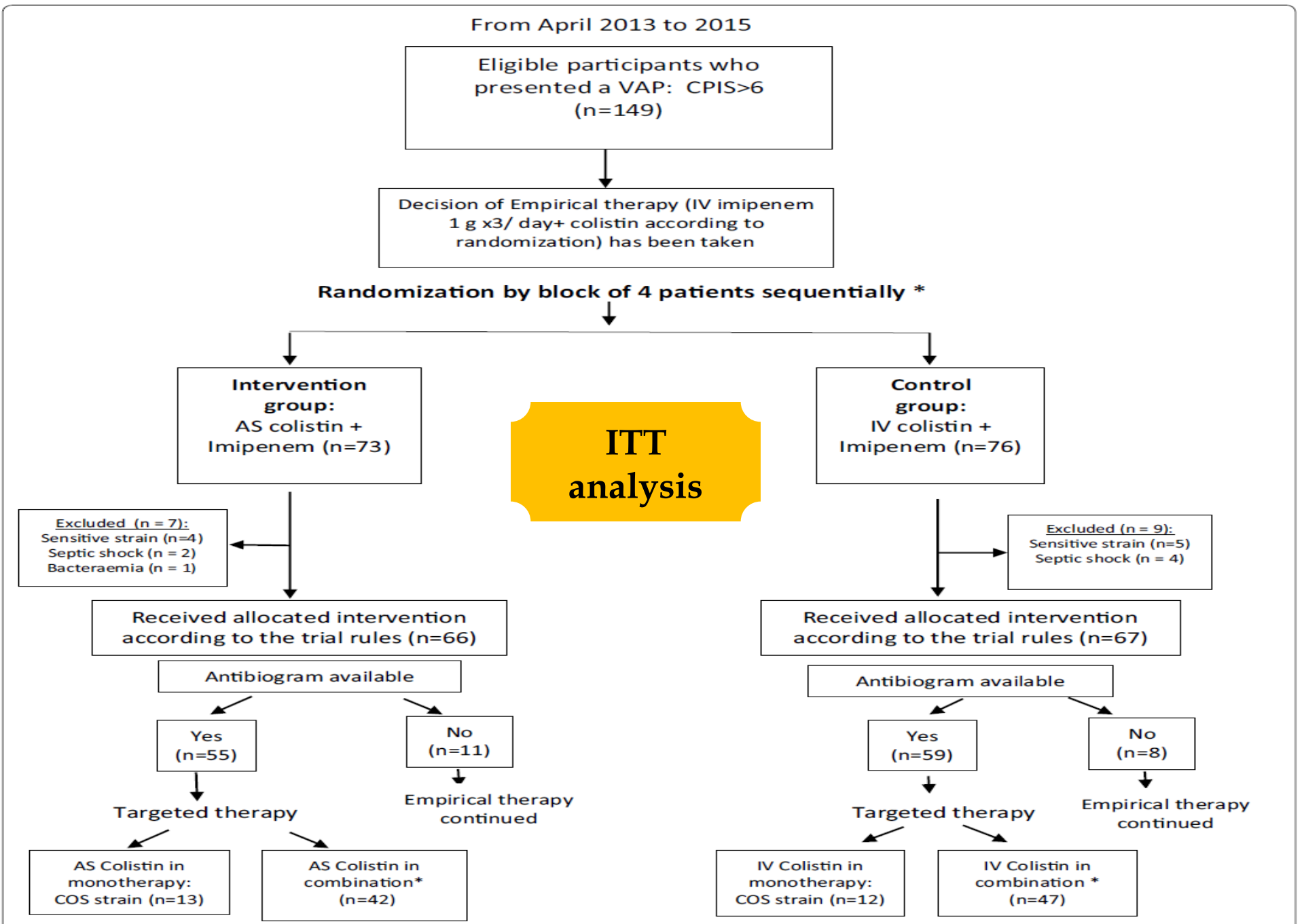


Fig. 1 Patients' flowchart. *VAP* ventilator-acquired pneumonia, *CPIS* Clinical Pulmonary Infection Score, *AS* aerosolised, *IV* intravenous, *COS* colistin-only susceptible. *The order of randomization was as follows: Block 1: AS, AS, IV, IV; Block 2: AS, IV, AS, IV; Block 3: IV, IV, AS, AS; Block 4: IV, AS, IV, AS. Details of combination are displayed in Table 1

Table 1 Baseline demographic and patients' clinical characteristics

	AS colistin group ($n = 73$)	IV colistin group ($n = 76$)	p value
Age: age (mean ± SD)	50 ± 16	53 ± 17	0.28
Sex ratio	2.31	1.81	0.49
SAPS II at inclusion	39 ± 13	40 ± 14	0.65
SOFA at inclusion	7.03 ± 3.8	6.5 ± 4.1	0.43
Reasons for admission [*n* (%)]			
Respiratory distress	32 (44 %)	29 (38 %)	
Neurological causes	23 (31.5 %)	26 (34 %)	
Metabolic disorders	11 (15 %)	15 (20 %)	
Intoxications	5 (7 %)	3 (4 %)	
Others	2 (2.5 %)	3 (4 %)	0.92
Length of stay before inclusion: days [mean ± SD (median)]	11.28 ± 9 (9)	11.14 ± 8.8 (9)	0.49
Previous antibiotic use [*n* (%)]	49 (67 %)	46 (60 %)	1
Colistin in monotherapy [*n* (%)]	13 (17.8 %)	12 (15.7 %)	1
Co-administered antibiotics [*n* (%)]	60 (80.3 %)	64 (82 %)	0.62
β-lactams	32	37	1
Aminoglycosides	11	12	1
Quinolones or macrolides	5	6	0.79
Tygecyclin	8	8	0.58
Glycopeptides	8	6	
Iodinated contrast agent	14 (19 %)	17 (22.3 %)	0.68

AS aerosolised, *IV* intravenous, *SAPS II* Simplified Acute Physiology Score II, *SOFA* Sequential Organ Failure Assessment, *SD* standard deviation

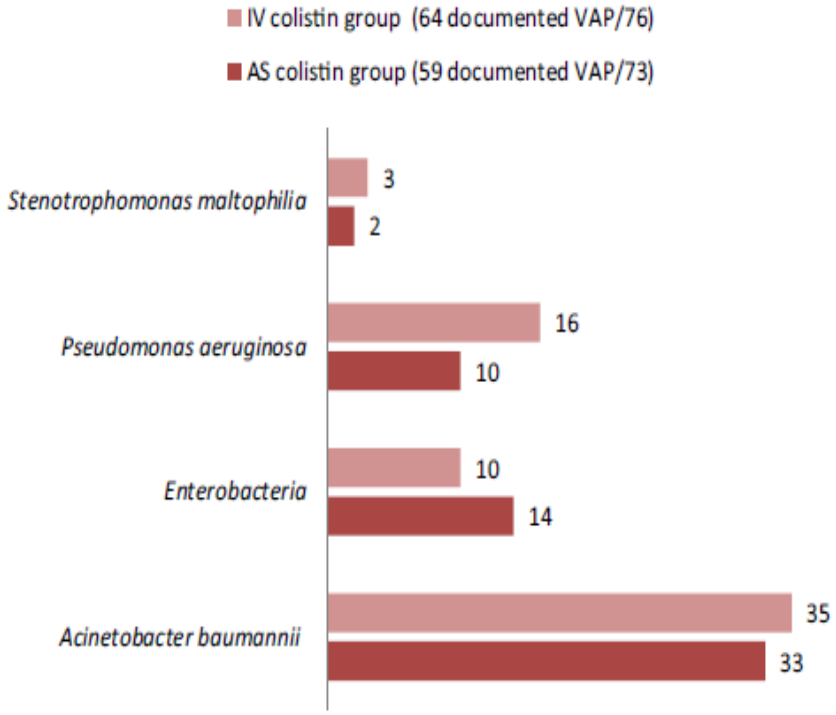


Fig. 2 Microorganism's distribution in study groups

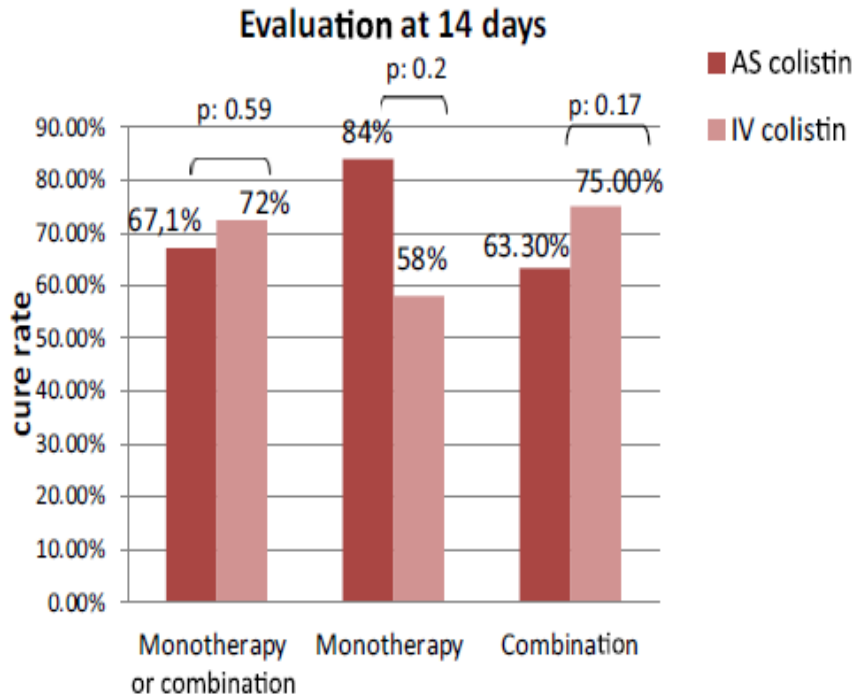
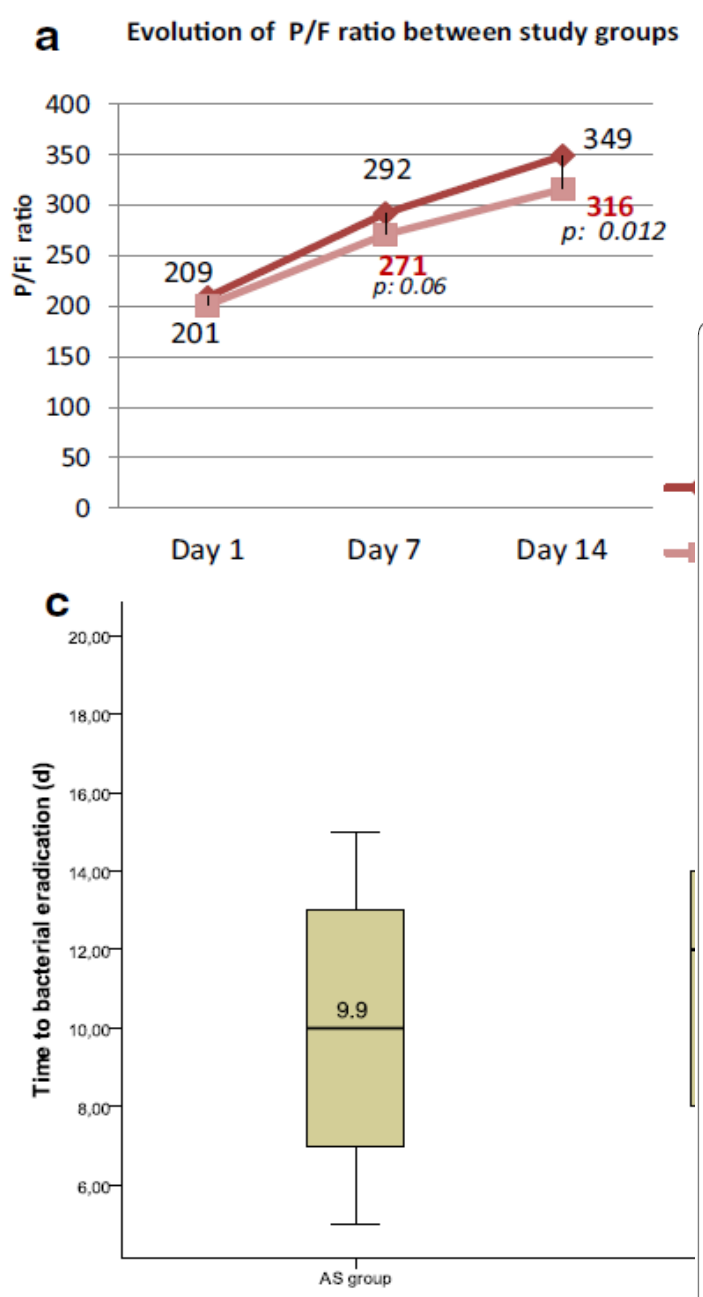


Fig. 3 Cure rates between the study groups. The cure rates were shown when colistin was prescribed in monotherapy, in combination or both



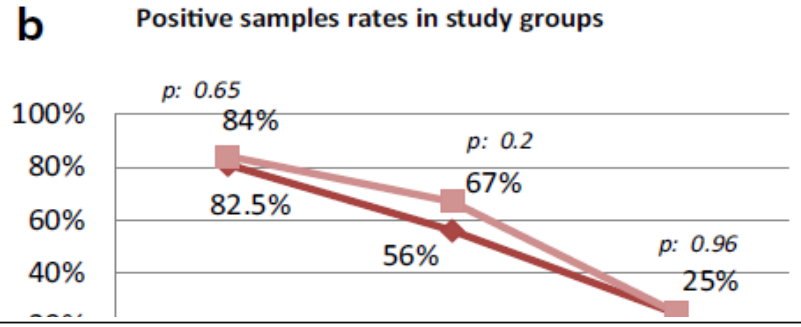


Fig. 4 **a** Evolution of *P/F* ratio in both groups. **b** Evolution of p
(TBE) between groups

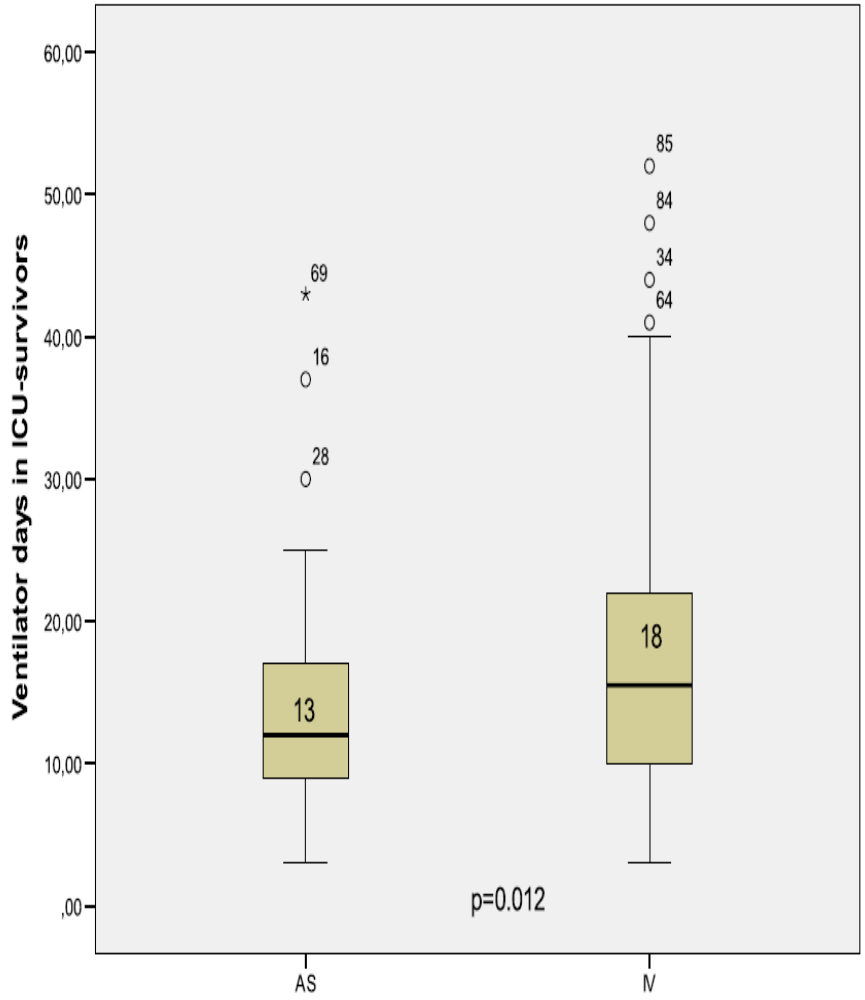


Fig. 7 Duration of mechanical ventilation in study groups

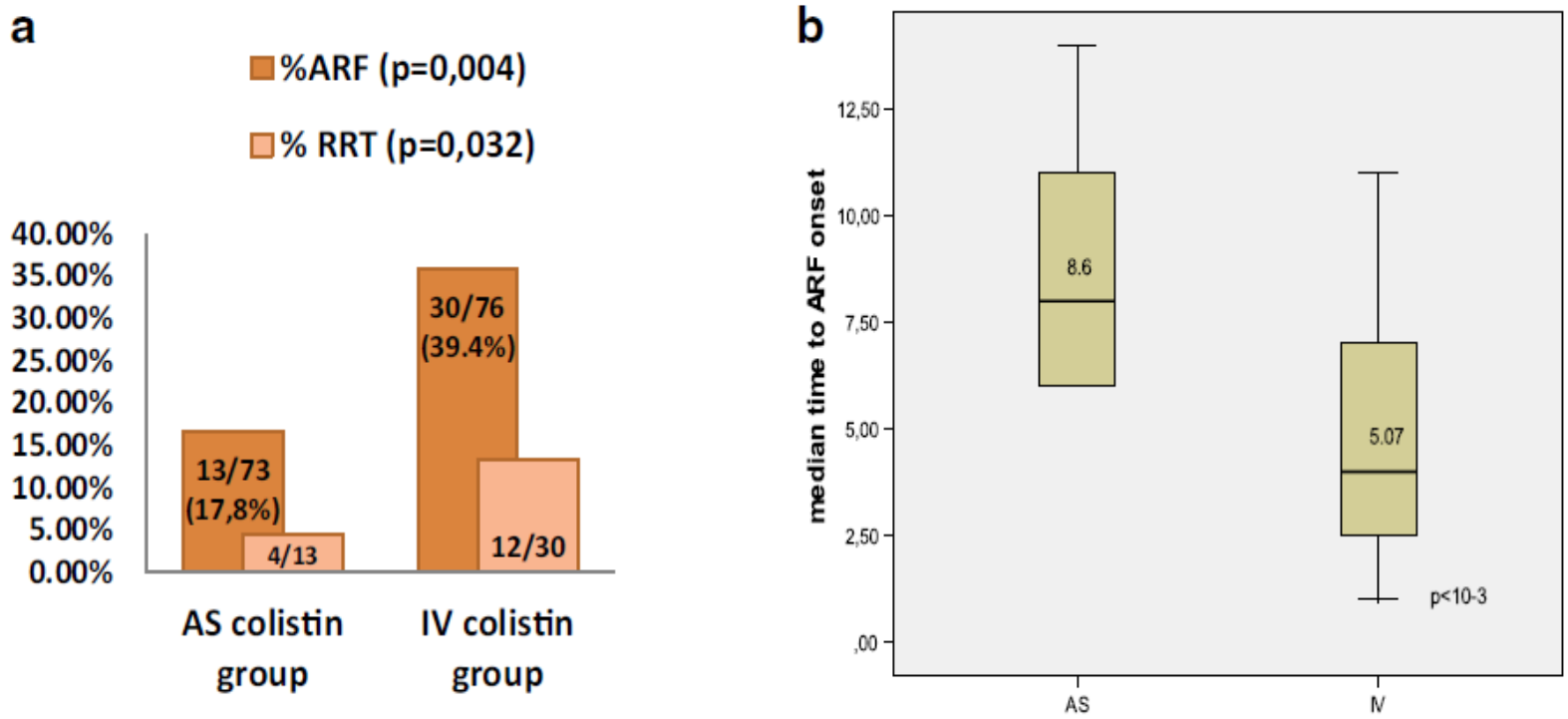


Fig. 5 **a** Incidence of acute renal failure (ARF) and necessity of replacement renal therapy (RRT) in both groups. **b** Mean time to ARF onset in both groups

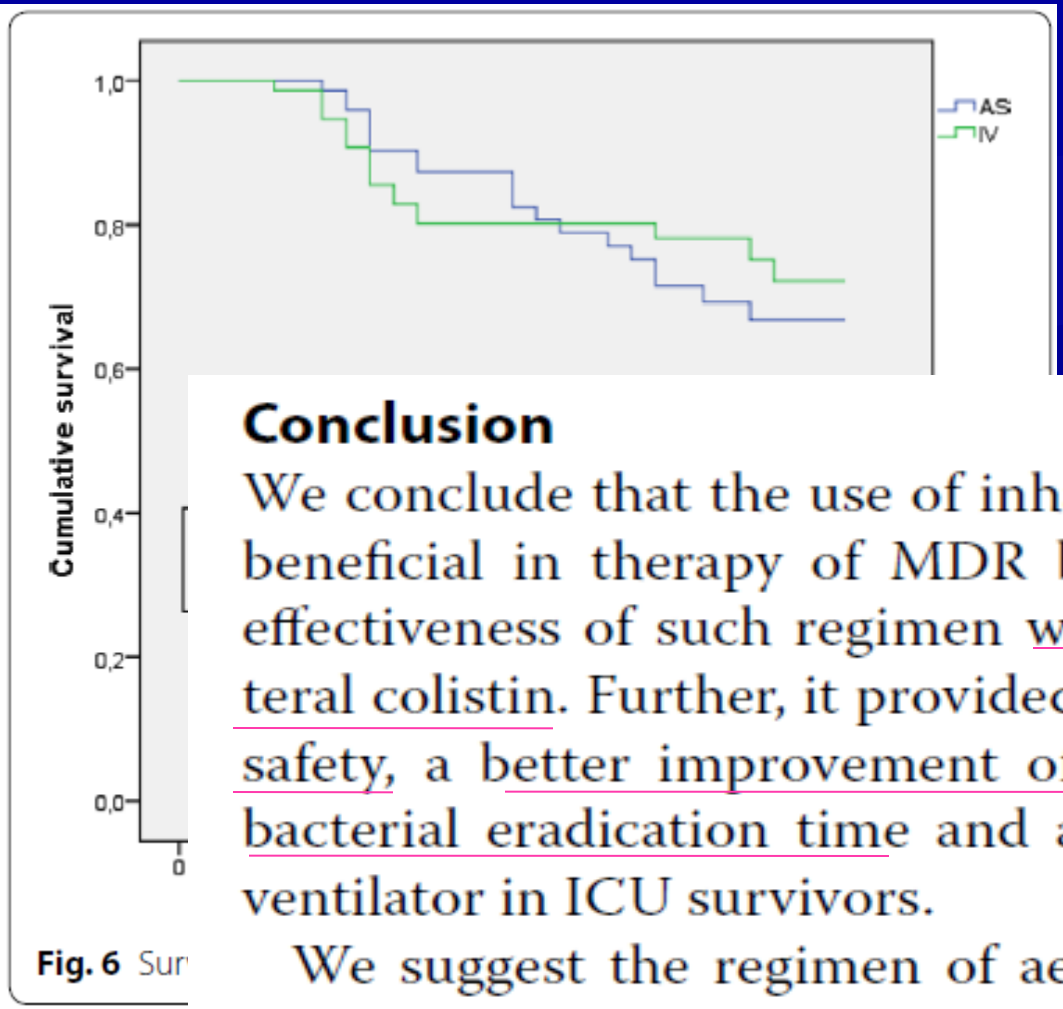


Fig. 6 Sur

Conclusion

We conclude that the use of inhaled colistin seems to be beneficial in therapy of MDR bacilli VAP. Therapeutic effectiveness of such regimen was as effective as parenteral colistin. Further, it provided several benefits: a renal safety, a better improvement of *P*/*F* ratio, a shortened bacterial eradication time and an earlier weaning from ventilator in ICU survivors.

We suggest the regimen of aerosolised colistin as the first-line therapy in VAP due to MDR bacilli outside a septic shock and/or bacteraemia.

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Implications cliniques:

- Les nébulisations répétitives (3-4/j) assurent des doses intra parenchymateuses résiduelles importantes: une condition qui peut limiter la sélection des souches résistantes
- Cette voie permet de réduire la colonisation des voies respiratoires supérieures (action efficace contre l'inoculum bactérien provenant de l'oropharynx)
- Conditions : doses+++ et type de nébuliseur+++